LIRAGLUTIDE E RISCHIO CARDIOVASCOLARE: DAL DIABETE ALL'OBESITA'

LUCA BUSETTO

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

LIRAGLUTIDE E RISCHIO CARDIOVASCOLARE: DAL DIABETE ALL'OBESITÀ'

Luca Busetto

Dipartimento di Medicina – DIMED
Università degli Studi di Padova

Centro per lo Studio ed il Trattamento Integrato dell'Obesità
Clinica Medica 3 - Azienda Ospedale Università Padova

Coordinatore della Obesity Management Task Force
European Association for the Study of Obesity

Presidente Eletto della Società Italiana delll'Obesità (SIO)

UNIVERSITÀ DEGLI STUDI DI PADOVA

EASOCOM
EASO Collaborating Centre for Obesity Management

EASO
European Association for the Study of Obesity

SIO
Società Italiana dell'Obesità

Liraglutide e rischio cardiovascolare: dal diabete all'obesità

TOPICS

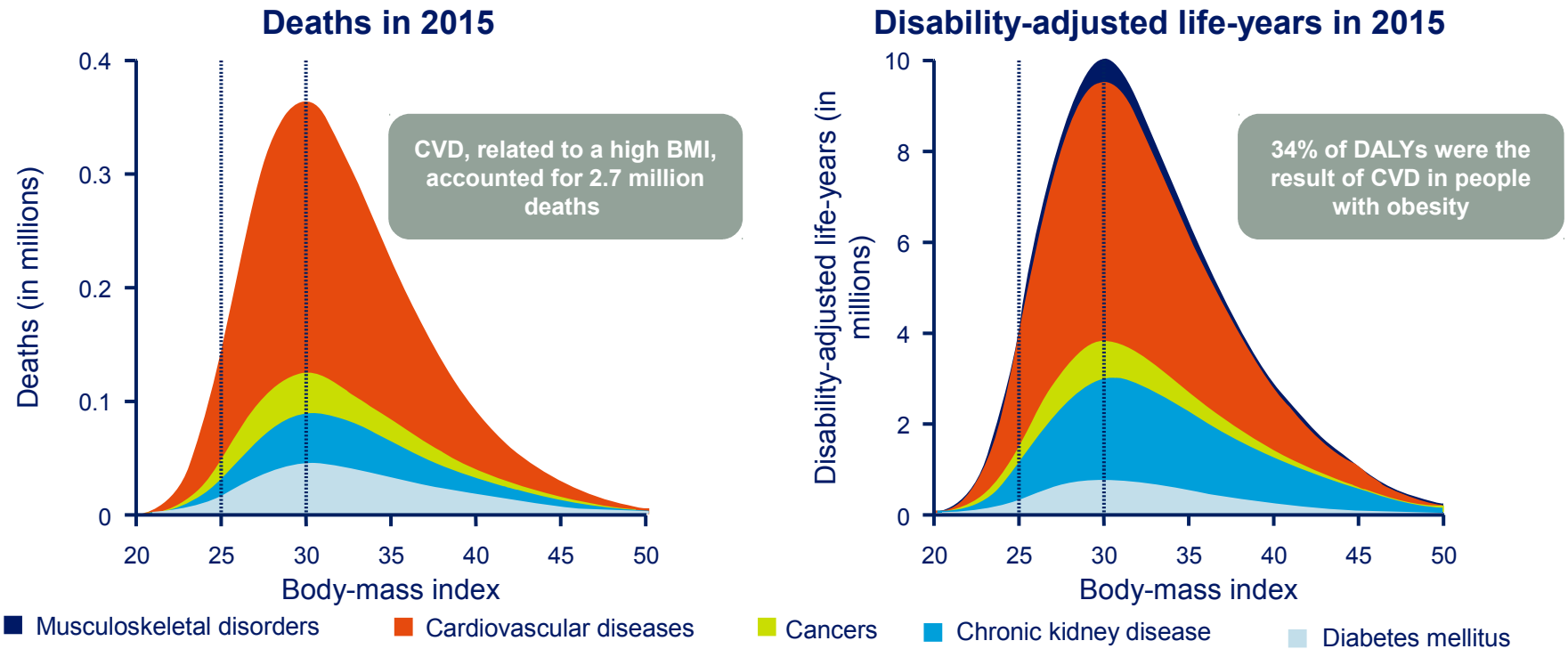
- Rischio cardiovascolare nel diabete e nell'obesità
- Liraglutide: meccanismi d'azione
- Liraglutide e rischio cardiovascolare nel paziente con diabete tipo 2
- Liraglutide nella terapia dell'obesità

Liraglutide e rischio cardiovascolare: dal diabete all'obesità

TOPICS

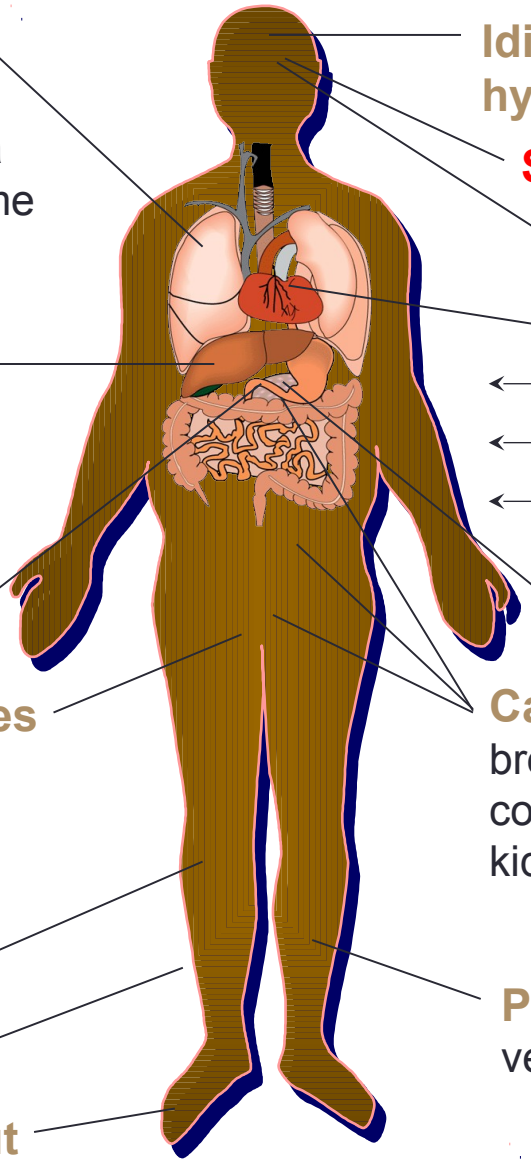
- Rischio cardiovascolare nel diabete e nell'obesità
- Liraglutide: meccanismi d'azione
- Liraglutide e rischio cardiovascolare nel paziente con diabete tipo 2
- Liraglutide nella terapia dell'obesità

Increasing BMI contributes to death and disability



GBD 2015 Obesity Collaborators *N Engl J Med* 2017;377:13–27

Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Idiopathic intracranial hypertension

Stroke

Cataracts

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

Gall bladder disease

Severe pancreatitis

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

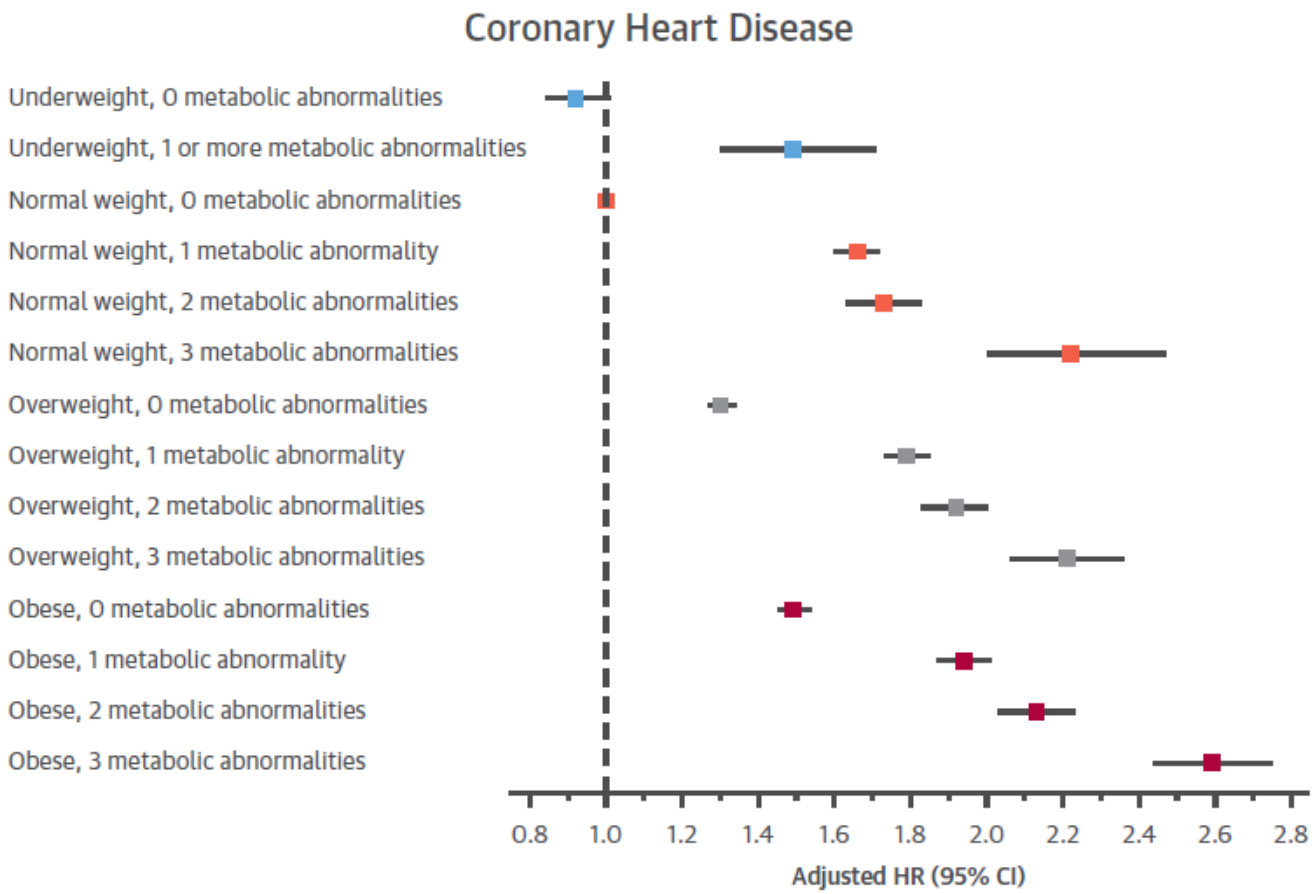
Osteoarthritis

Skin

Gout

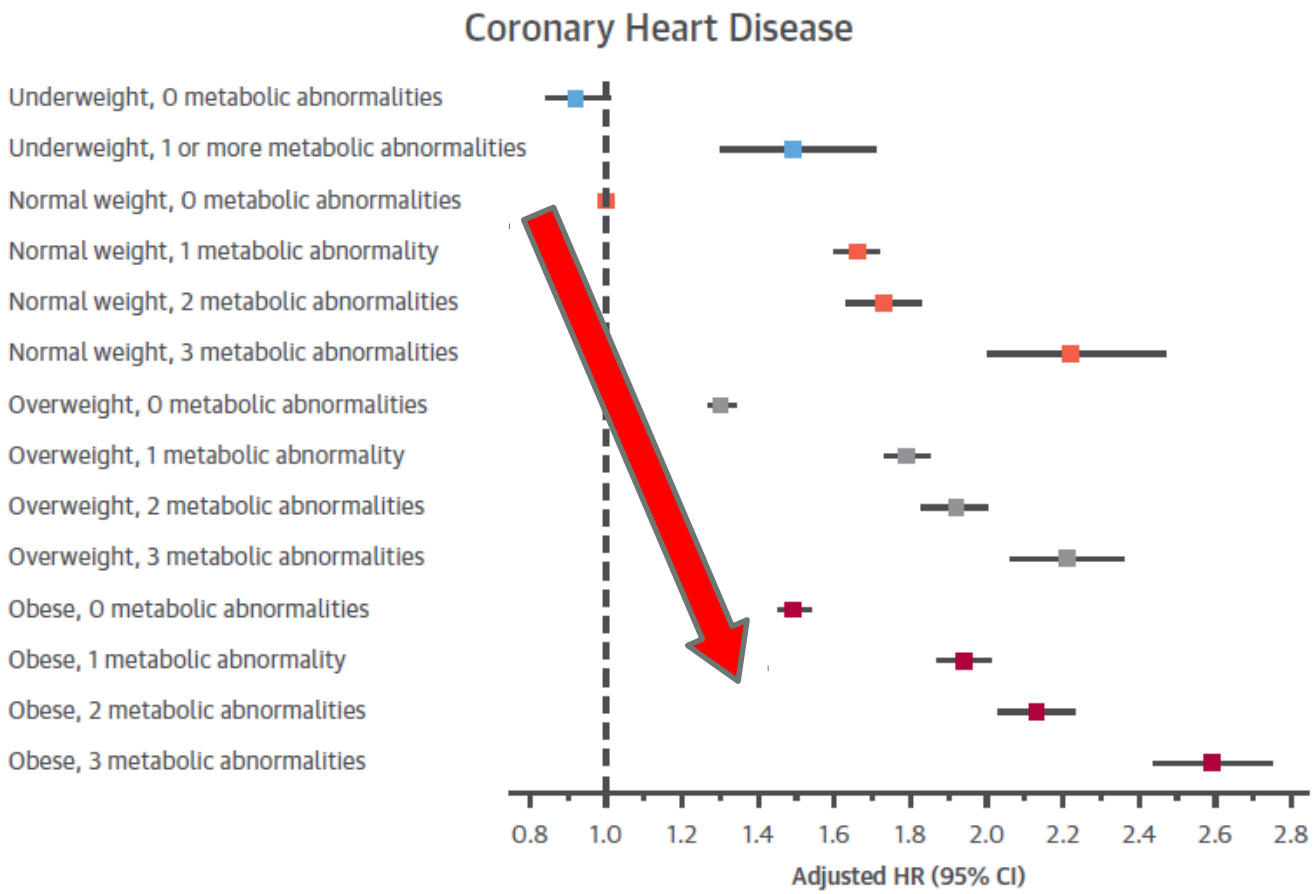
Phlebitis
venous stasis

Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women

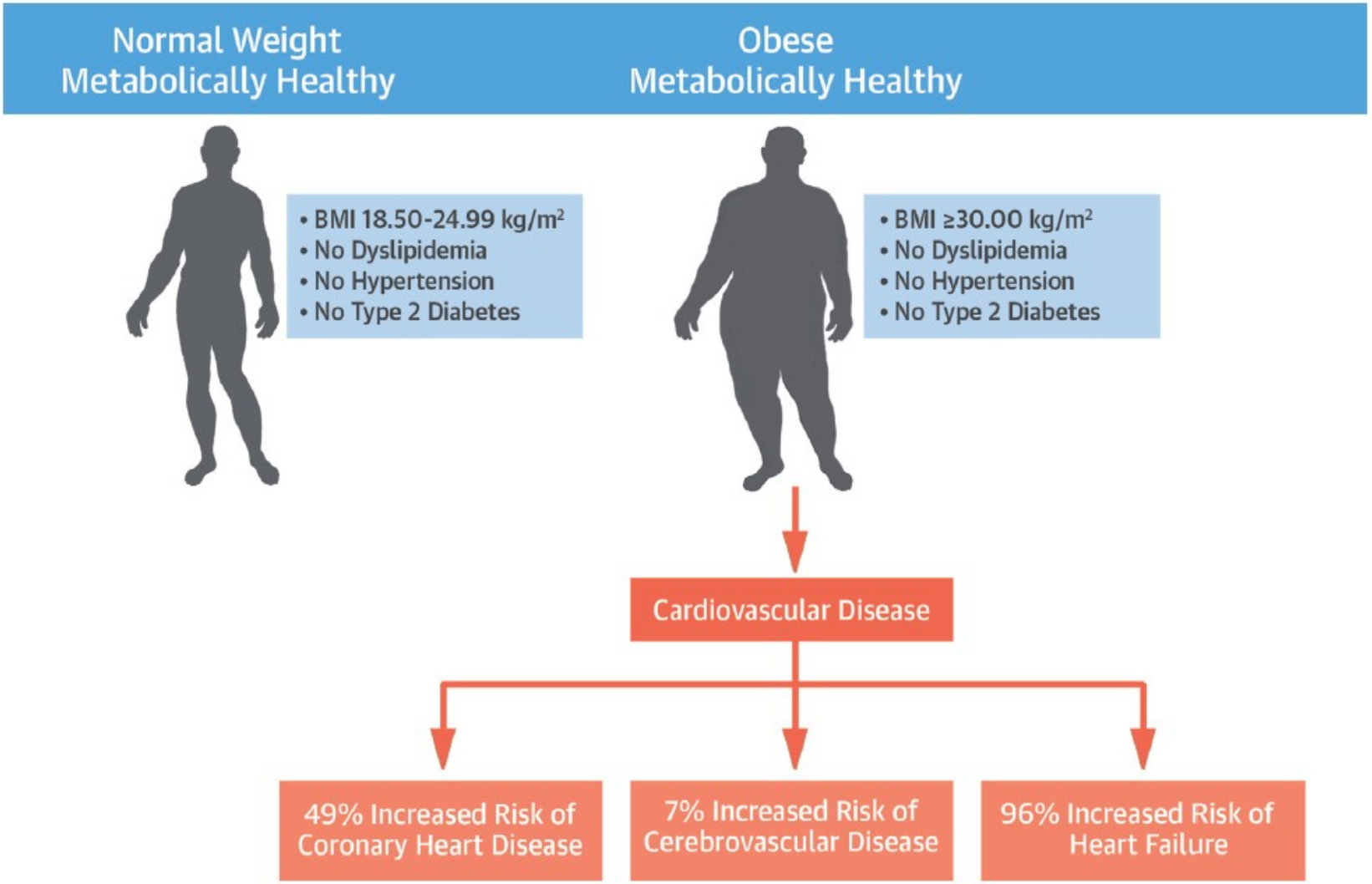


Caleyachetty R et l. *Am Coll Cardiol* 2017;70:1429-37

Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women



Caleyachetty R et l. *Am Coll Cardiol* 2017;70:1429-37

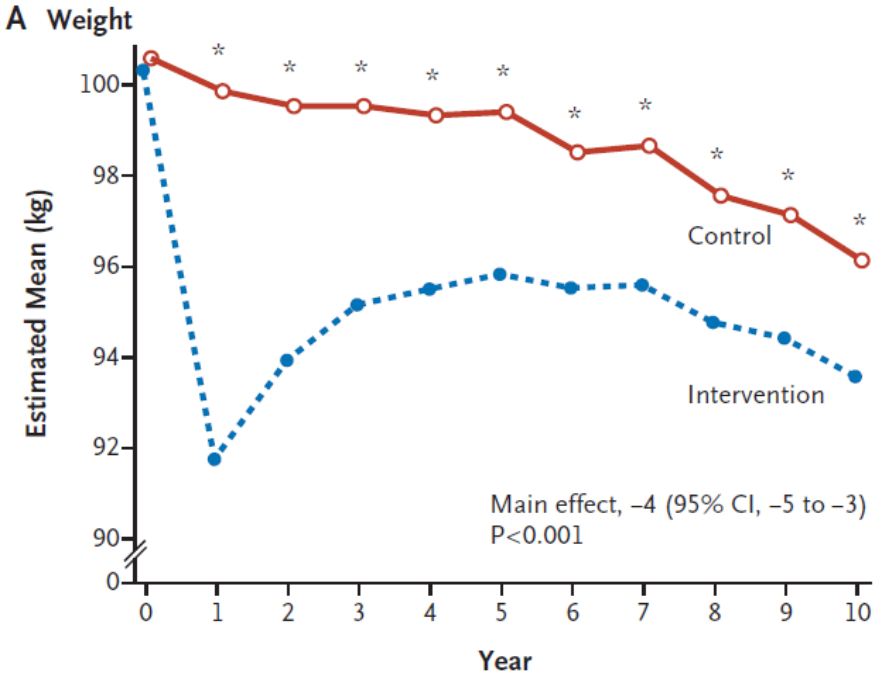


Caleyachetty, R. et al. J Am Coll Cardiol. 2017;70(12):1429-37.

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

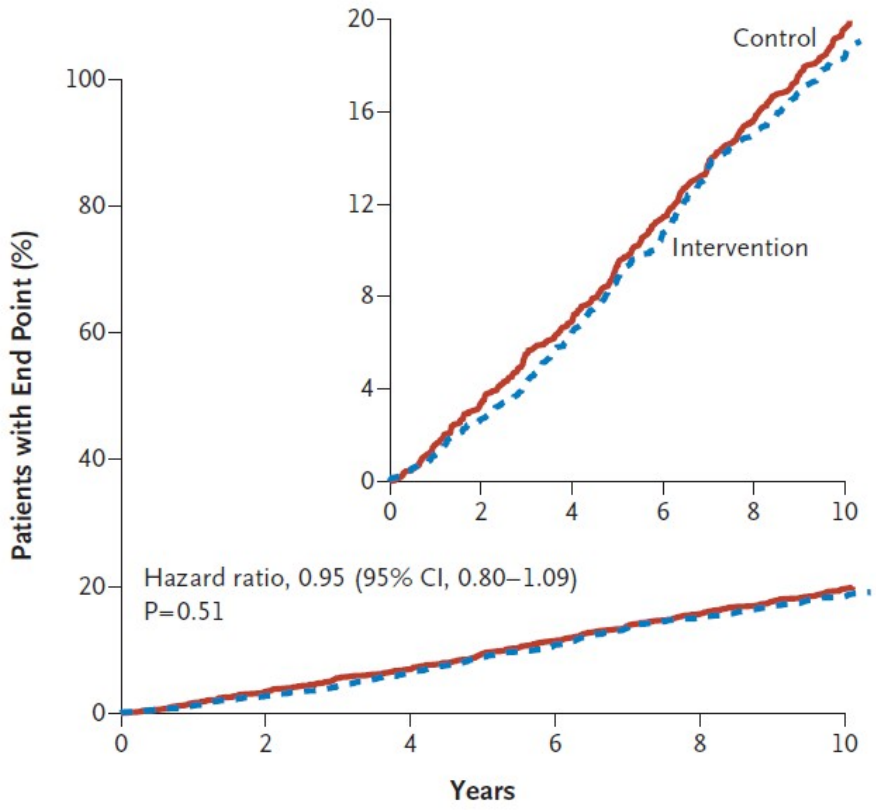
Control group (N. 2575 with T2DM):	Standard diabetes support and education.
Intervention group (N. 2570 with T2DM):	Intensive lifestyle interventiom



NEJM 2013;369:145-154

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*



No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

NEJM 2013;369:145-154

Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial

	Weight-change categories (percentage weight loss in first year; n=4834)				
	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	p value
Primary outcome					
Events per person-years	289/17 075	141/7870	154/8570	128/8942	..
Crude rate per 100 person-years	1·69	1·79	1·80	1·43	..
Unadjusted hazard ratio (95% CI)	1·00	1·07 (0·88–1·31)	1·07 (0·88–1·31)	0·83 (0·67–1·02)	0·21
Adjusted hazard ratio†(95% CI)	1·00	1·08 (0·88–1·33)	1·16 (0·95–1·42)	0·79 (0·64–0·98), p=0·034*	0·17
Secondary outcome					
Events per person-years	422/16 699	206/7657	203/8411	186/8792	..
Crude rate per 100 person-years	2·53	2·69	2·41	2·12	..
Unadjusted hazard ratio (95% CI)	1·00	1·08 (0·91–1·27)	0·96 (0·81–1·13)	0·83 (0·70–0·99), p=0·035*	0·04
Adjusted hazard ratio† (95% CI)	1·00	1·05 (0·88–1·25)	0·97 (0·82–1·16)	0·76 (0·63–0·91), p=0·003*	0·006

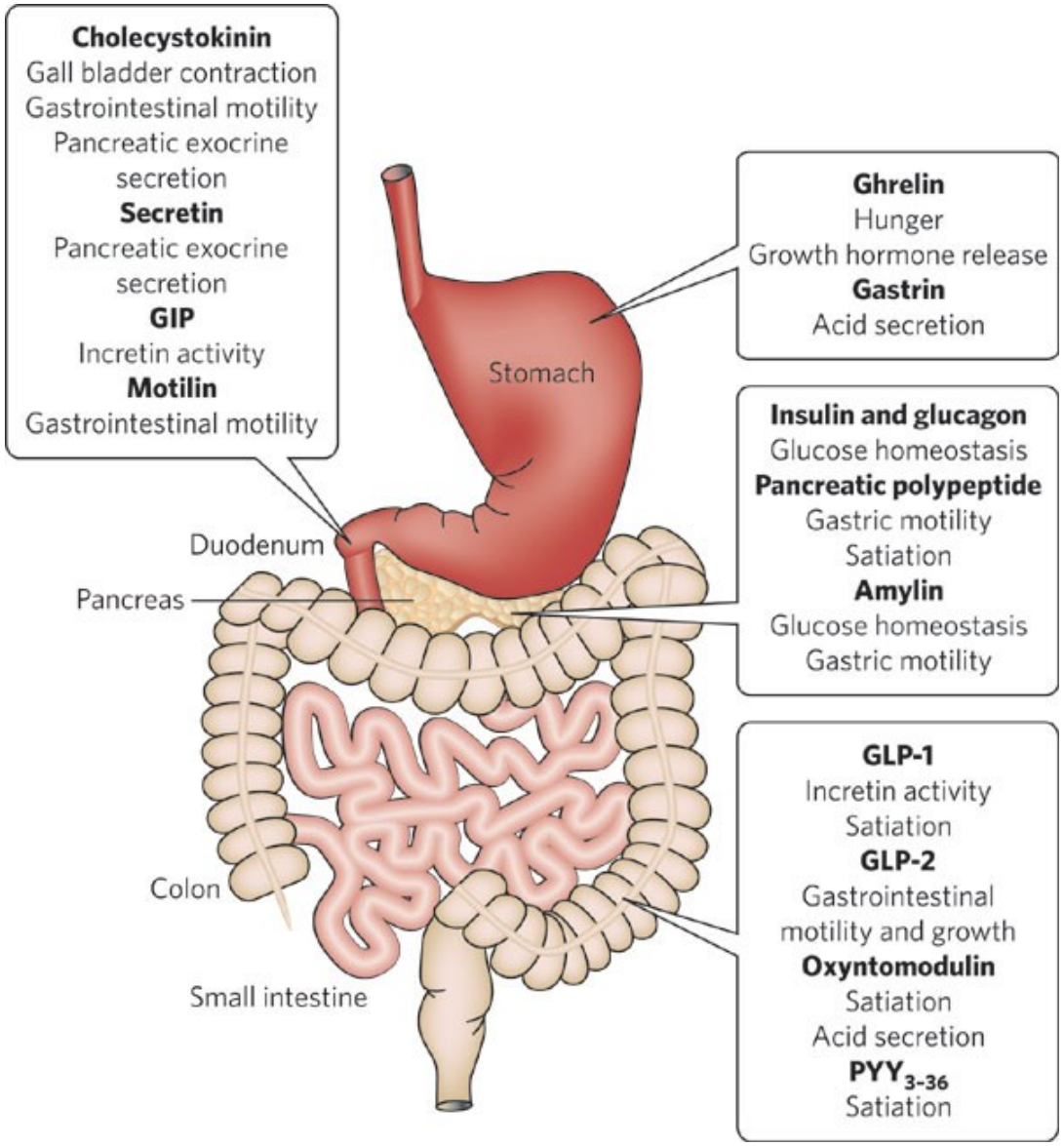
Lancet Endocrinol 2016;4:913-921

Liraglutide e rischio cardiovascolare: dal diabete all'obesità

TOPICS

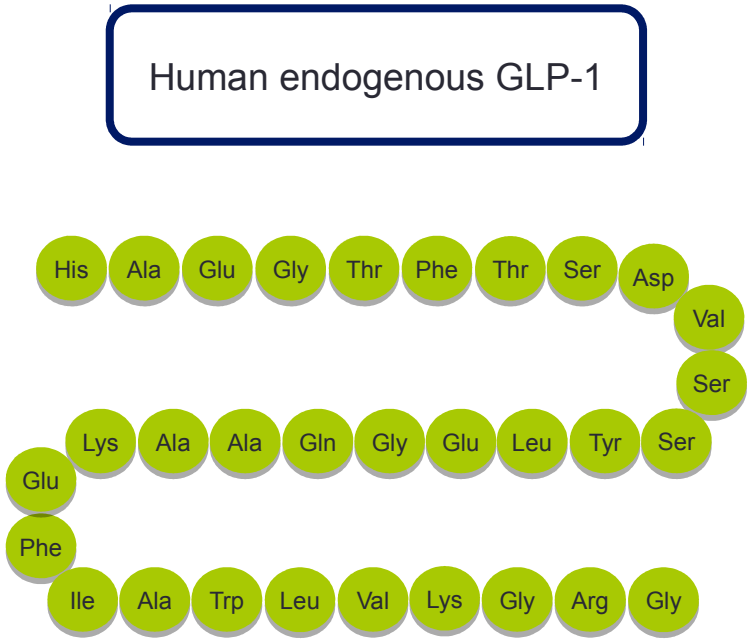
- Rischio cardiovascolare nel diabete e nell'obesità
- Liraglutide: meccanismi d'azione
- Liraglutide e rischio cardiovascolare nel paziente con diabete tipo 2
- Liraglutide nella terapia dell'obesità

Gut-brain hormonal interactions



What is GLP-1?

- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family
- Secreted predominantly from L-cells in the gut, but also the brain (nucleus tractus solitarius)

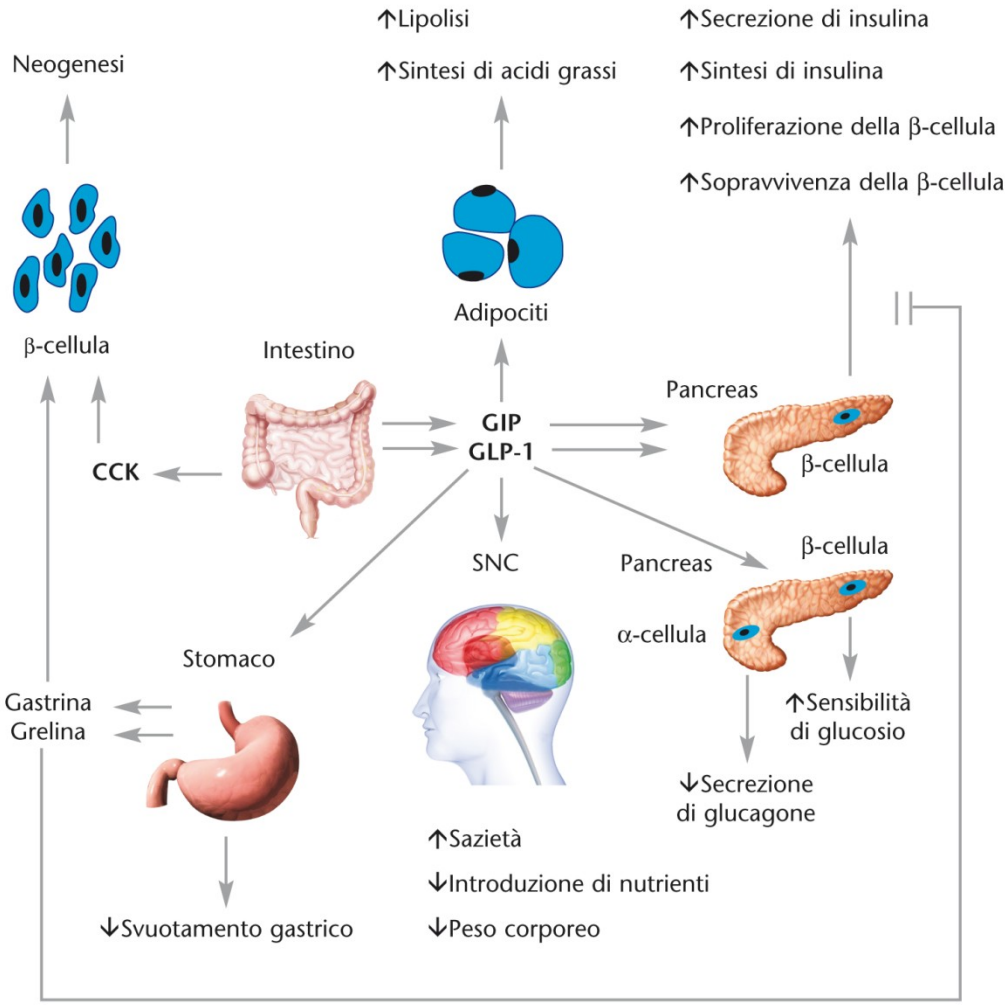


Enzymatic degradation by DPP-4

$t_{½}$=1.5–2 min

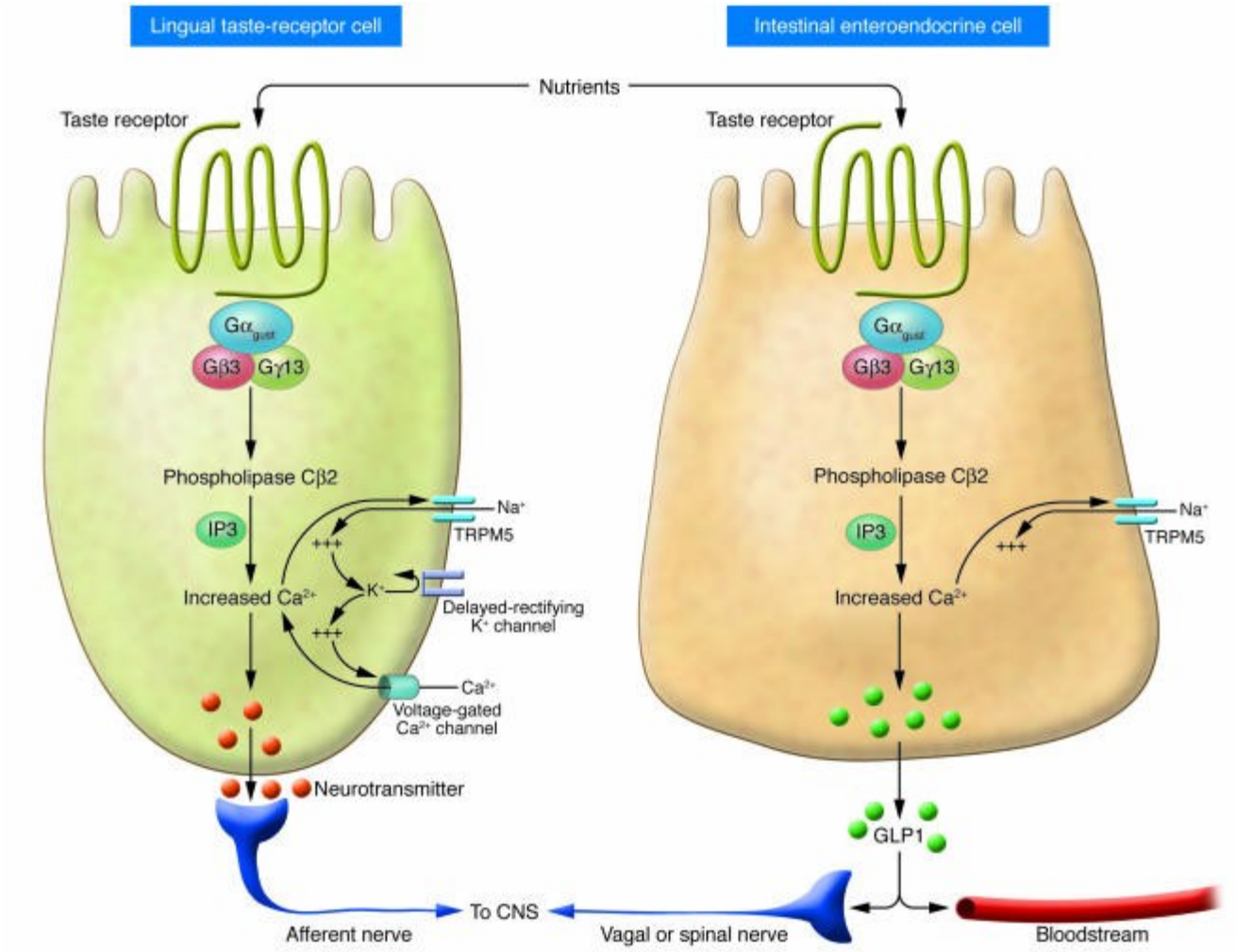
Merchenthaler *et al. J Comp Neurol* 1999;403:261–80
Baggio, Drucker. *Gastroenterology* 2007;132:2131–57
Ducker, Nauck. *Lancet* 2006;368:1696–705

Principali effetti di GLP-1

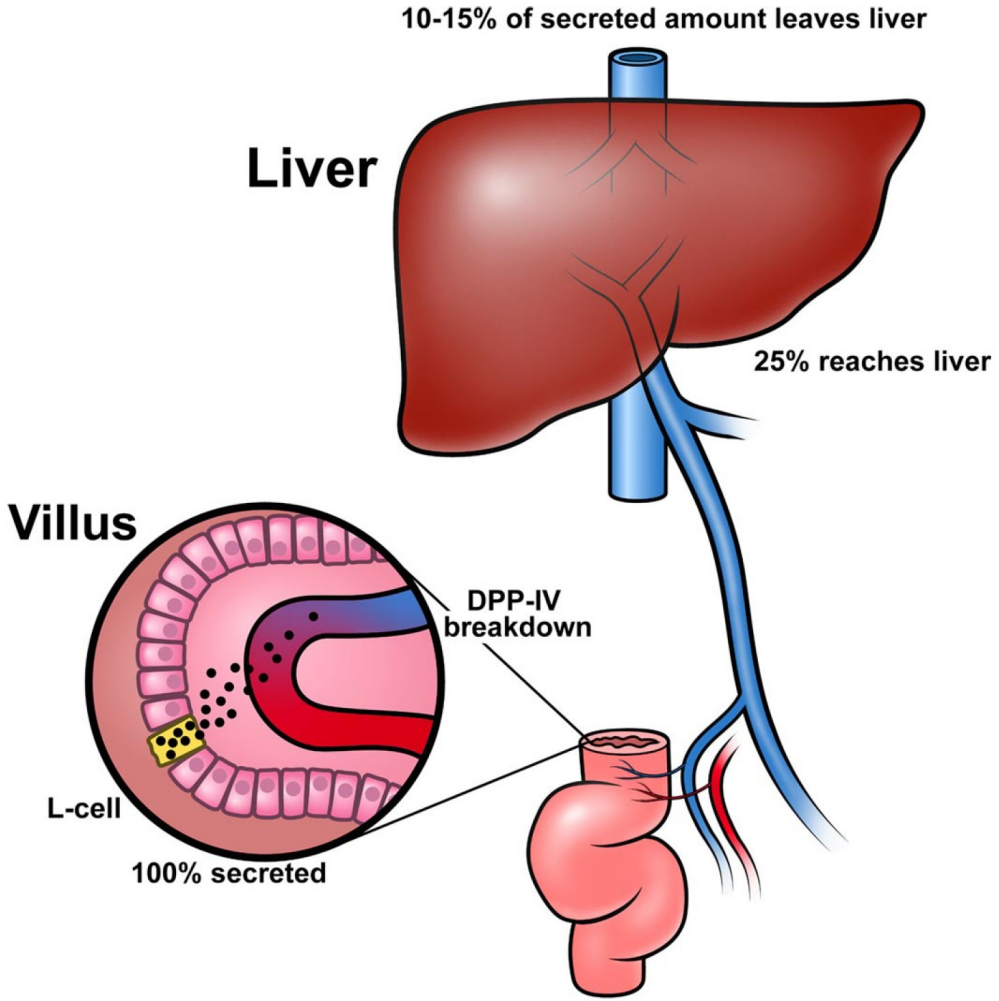


Gastrointestinal regulation of food intake

David E. Cummings and Joost Overduin



The Journal of Clinical Investigation January 2007


10-15% of secreted amount leaves liver
Liver
25% reaches liver
Villus
DPP-IV
breakdown
L-cell
100% secreted

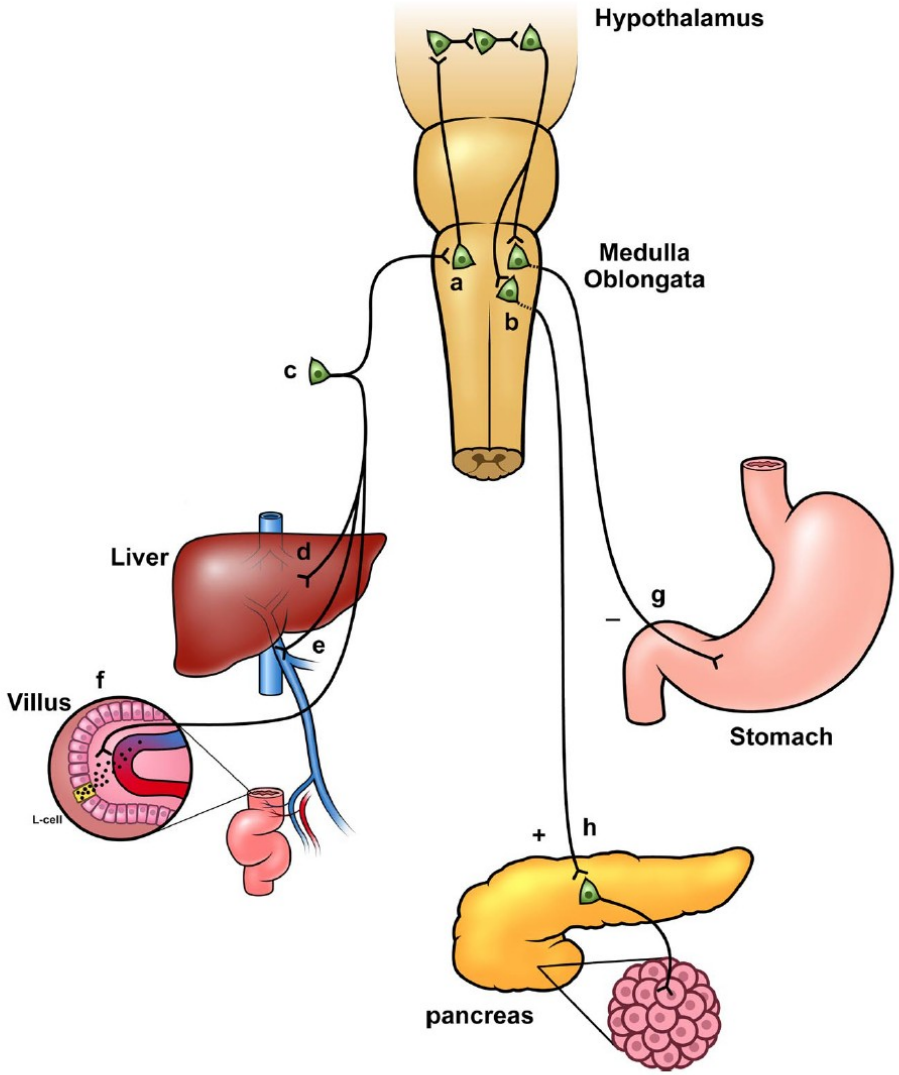
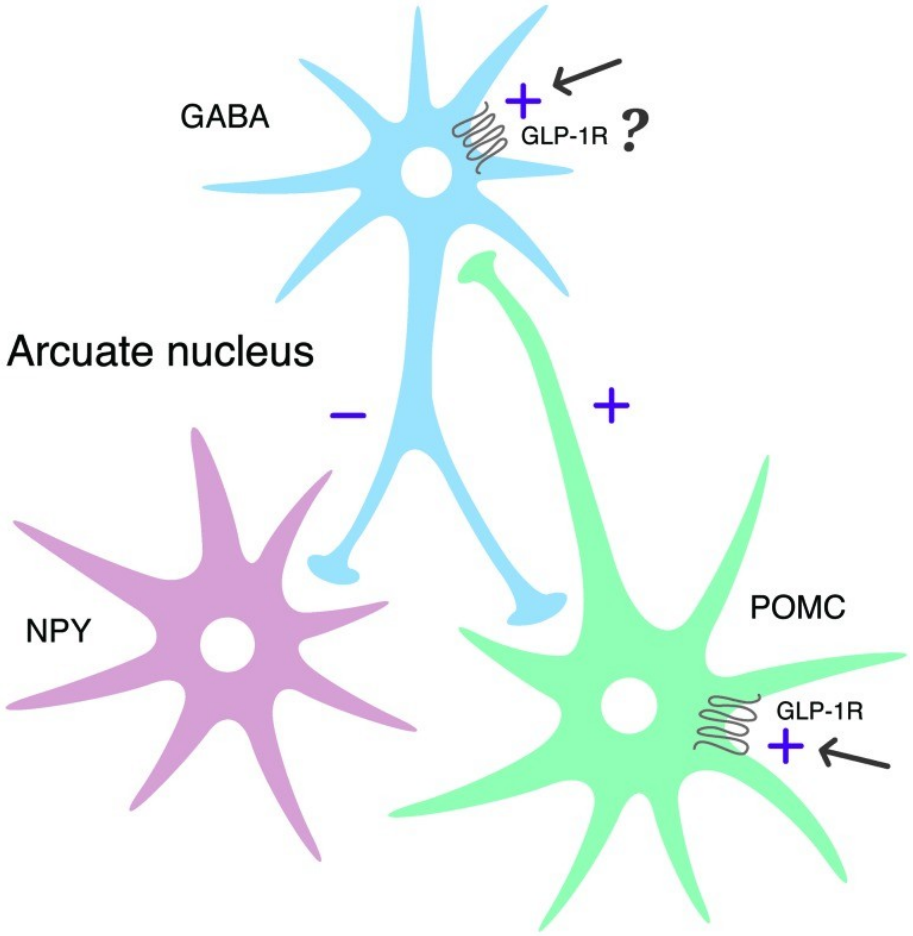


FIG. 9. The neural pathway for the actions of GLP-1. GLP-1 secretion is stimulated by nutrients in the gut lumen (a magnified intestinal villus with an open-type L-cell is shown at the *lower left*), and newly released GLP-1 diffuses across the basal lamina into the lamina propria. On its way to the capillary, however, it may bind to and activate sensory afferent neurons (*f*) originating in the nodose ganglion (*c*), which may in turn activate neurons of the solitary tract nucleus (*a*). The same neuronal pathway may be activated by sensory neurons in the hepatoportal region (29) (*e*) or in the liver tissue (39) (*d*). Ascending fibers from the solitary tract neurons may generate reflexes in the hypothalamus, and descending impulses (from neurons in the paraventricular nucleus?) may activate vagal motor neurons (*b*), that send stimulatory (*h*) or inhibitory (*g*) impulses to the pancreas and the gastrointestinal tract. Interactions between ascending sensory nerve fibers and vagal motorneurons may also take place at the level of the brain stem.

The Journal of Clinical Investigation October 2014

Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight

Laurie L. Baggio and Daniel J. Drucker



Liraglutide is a once-daily, human GLP-1 analogue

Human endogenous GLP-1

$T_{½}$= ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

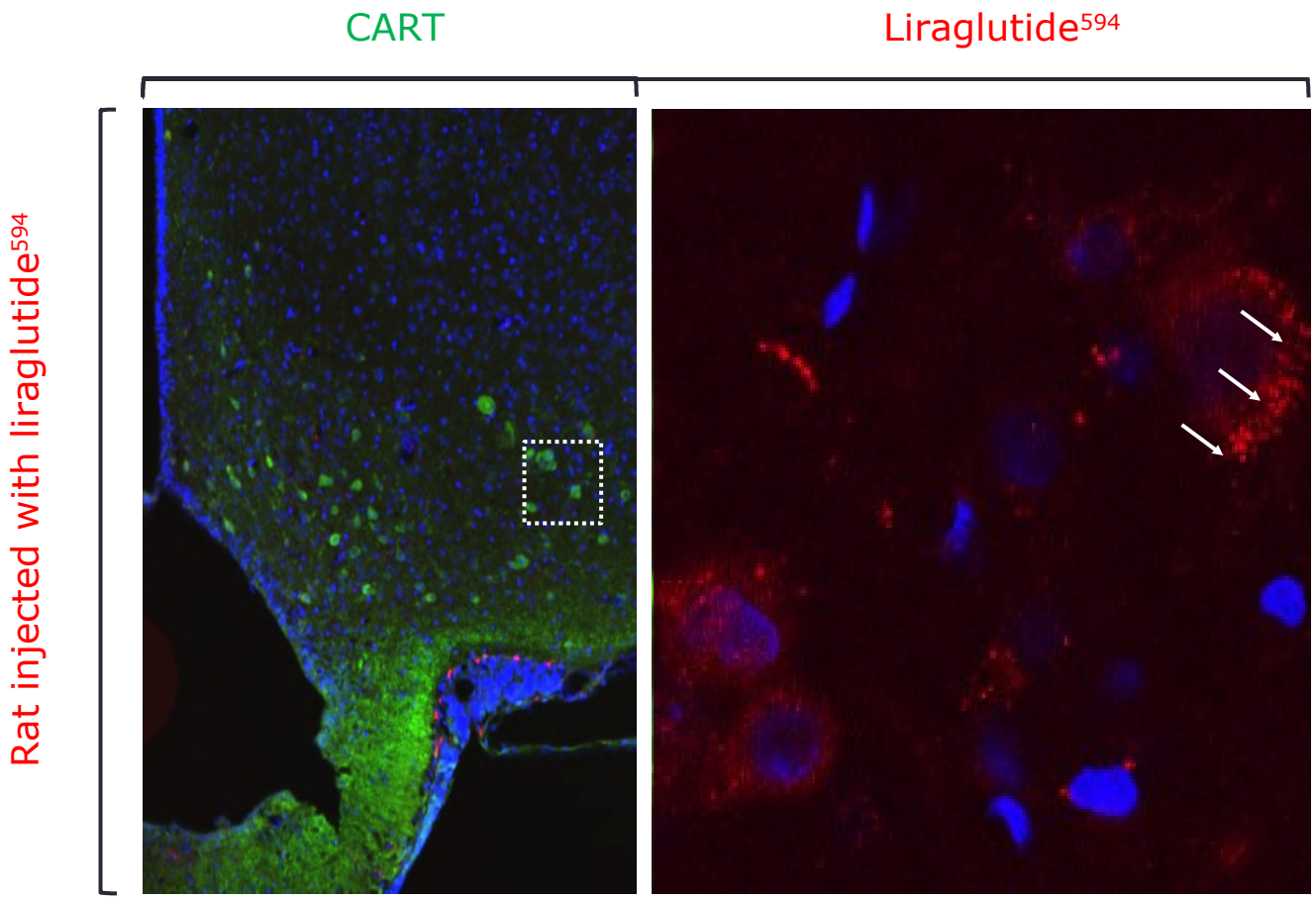
97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

↓

Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life
($T_{½}$=13 h)

Knudsen *et al. J Med Chem* 2000;43:1664–9;
Degn *et al. Diabetes* 2004;53:1187–94

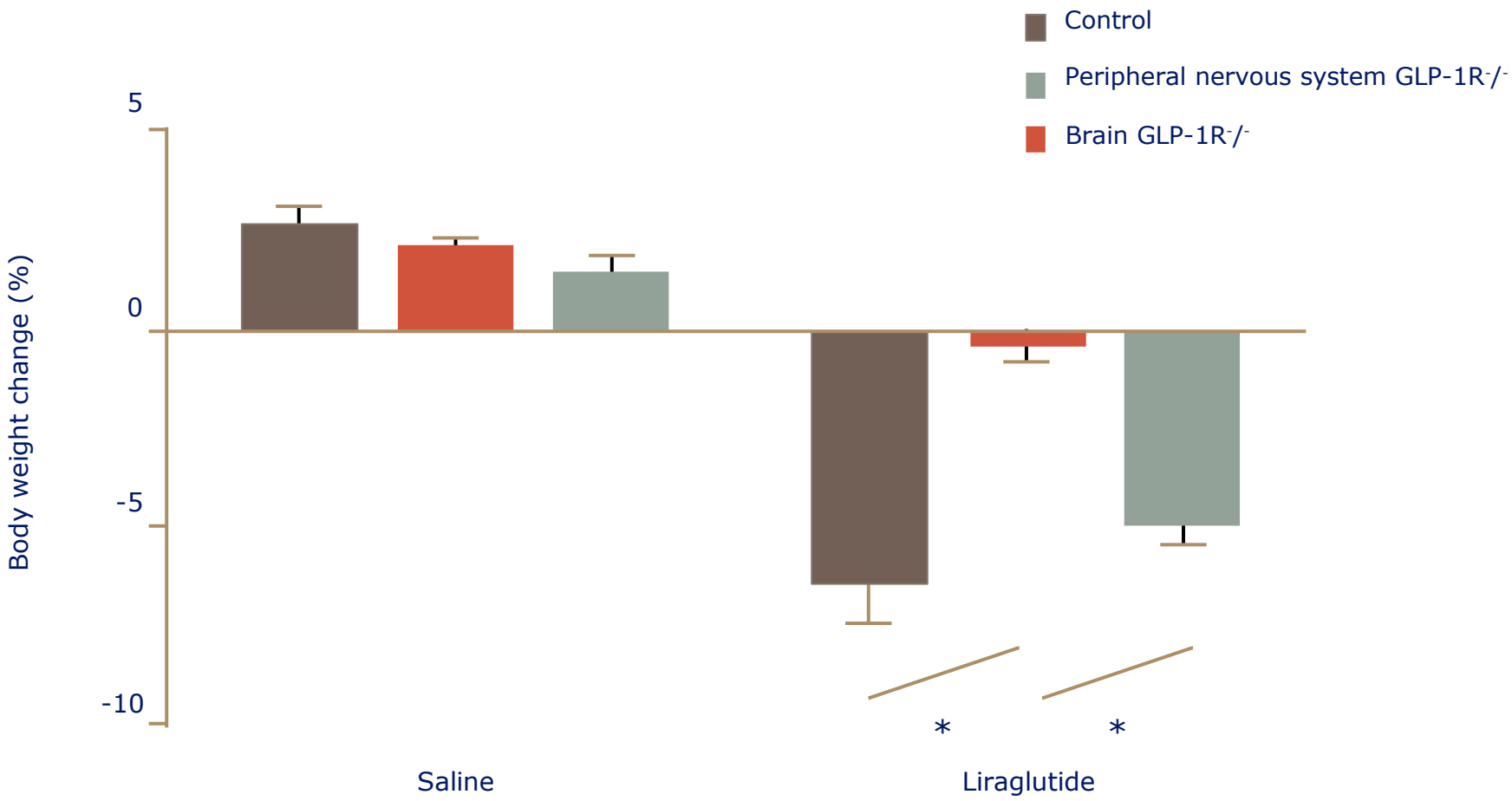
Liraglutide^{594} was localised in CART/POMC neurons in rat brain



Liraglutide^{594}, Alexa Fluor®594 C5-maleimide-liraglutide; CART, cocaine- and amphetamine-regulated transcript; POMC, pro-opiomelanocortin

Secher et al. J Clin Invest 2014;124:4473–88

Brain GLP-1 receptors mediate the body weight lowering effect of liraglutide



*P<0.05 compared with saline treatment, same genotype unless otherwise indicated

Sisley et al. J Clin Invest 2014;124:2456–63

Liraglutide e rischio cardiovascolare: dal diabete all'obesità

TOPICS

- Rischio cardiovascolare nel diabete e nell'obesità
- Liraglutide: meccanismi d'azione
- Liraglutide e rischio cardiovascolare nel paziente con diabete tipo 2
- Liraglutide nella terapia dell'obesità

LEADER
Liraglutide and cardiovascular ourcomes in type 2 diabetes

Major inclusion criteria

- Age ≥ 50 years with at least one cardiovascular coexisting condition:

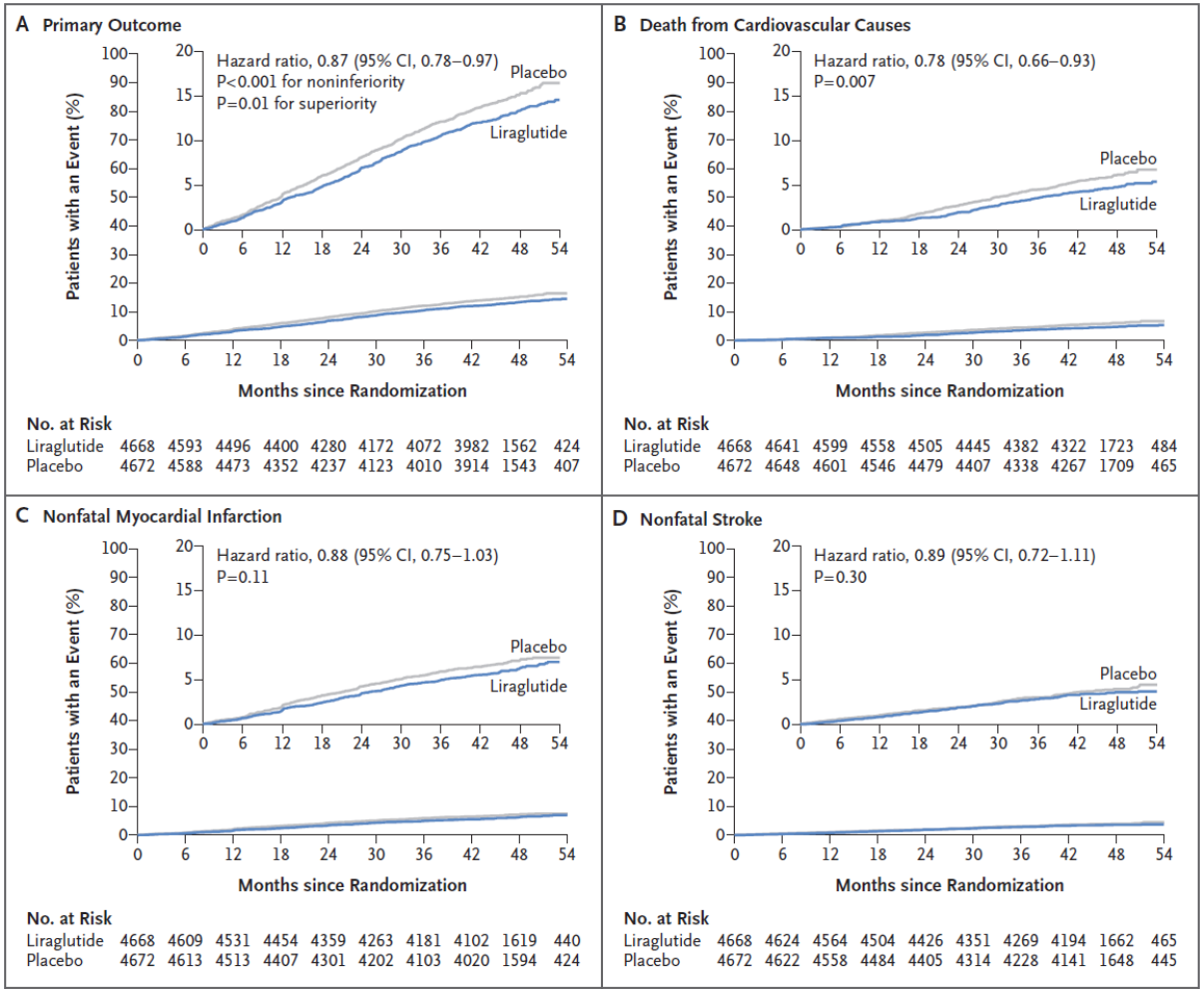
  coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, chronic heart failure of NYHA class II or III.

- Age ≥ 60 years with at least one cardiovascular risk factor

  microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, ankle–brachial index of less than 0.9.

Marso et al. NEJM 2016;375:311-22

LEADER
Liraglutide and cardiovascular ourcomes in type 2 diabetes



Marso et al. NEJM 2016;375:311-22

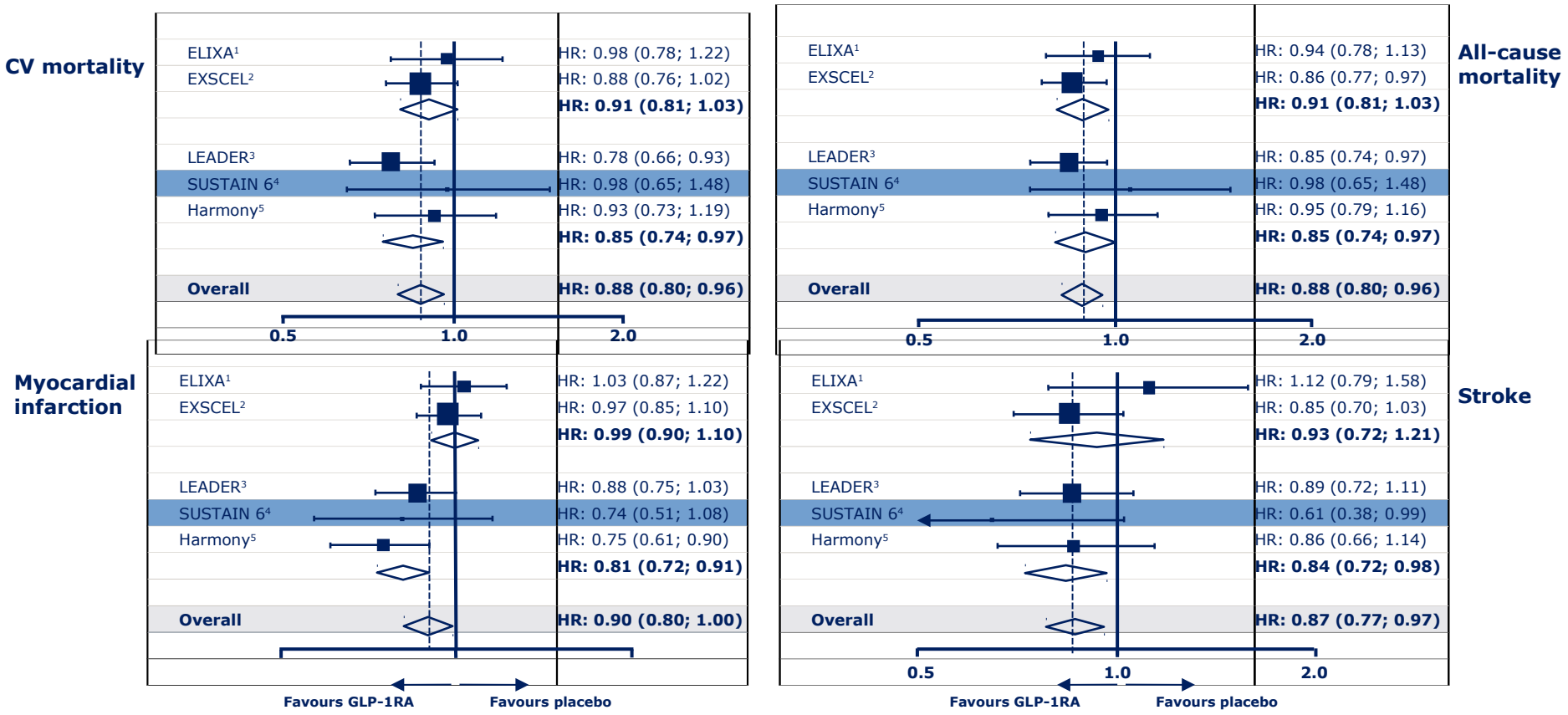
LEADER
Liraglutide and cardiovascular ourcomes in type 2 diabetes

Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia†	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

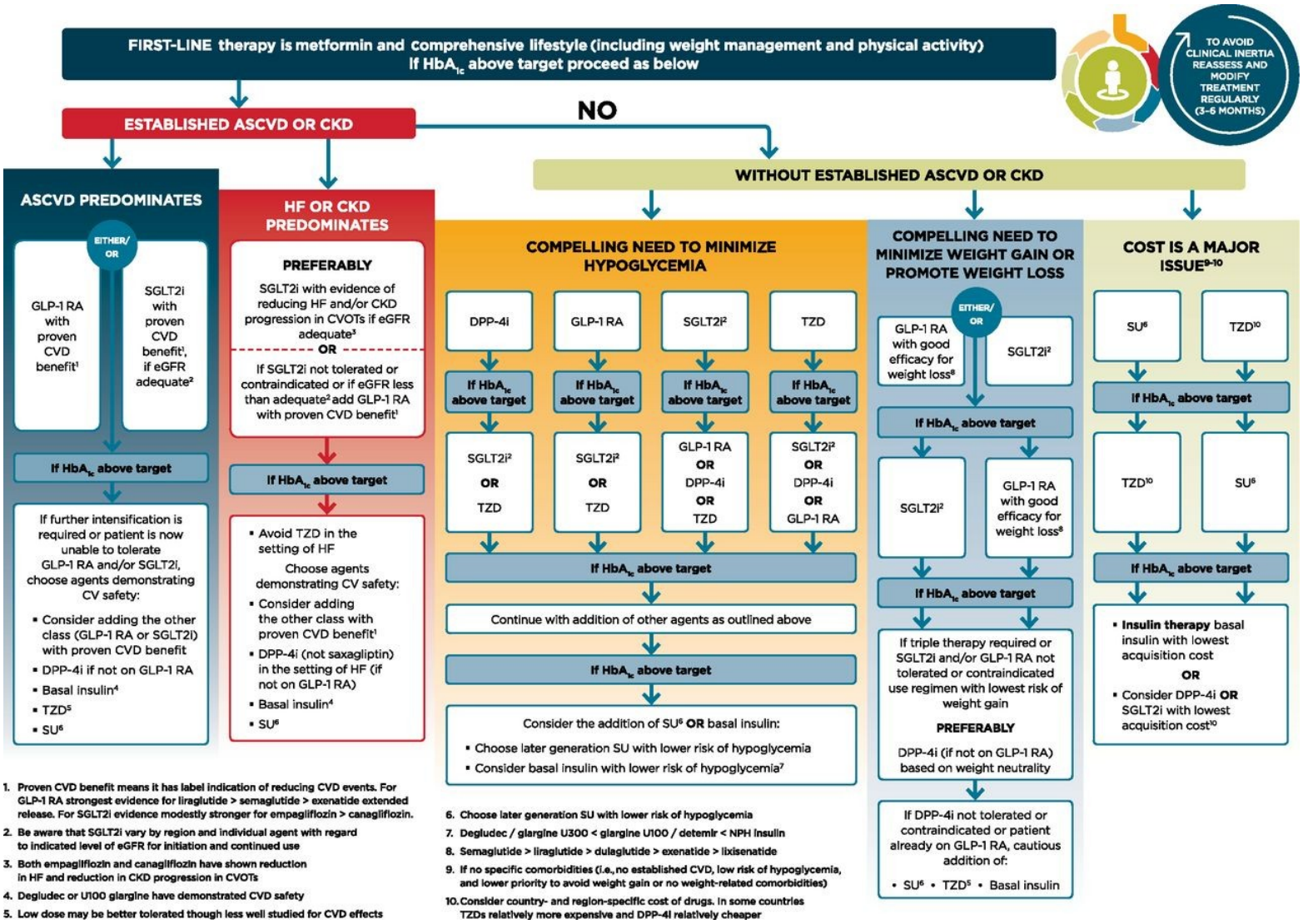
Marso et al. NEJM 2016;375:311-22

CVD Outcome studies with GLP-1RA



1. **Lixisenatide** Pfeffer M et al. *N Engl J Med* 2015;373:2247–57. 2. **Exenatide** Holman RR et al. *N Engl J Med* 2017;377:1228–1239; 3. **Liraglutide** Marso SP et al. *N Engl J Med* 2016;375:311–322; 4. **Semaglutide** Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 5. **Albiglutide** Hernandez AF et al. *Lancet* 2018;392:1519–1529

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



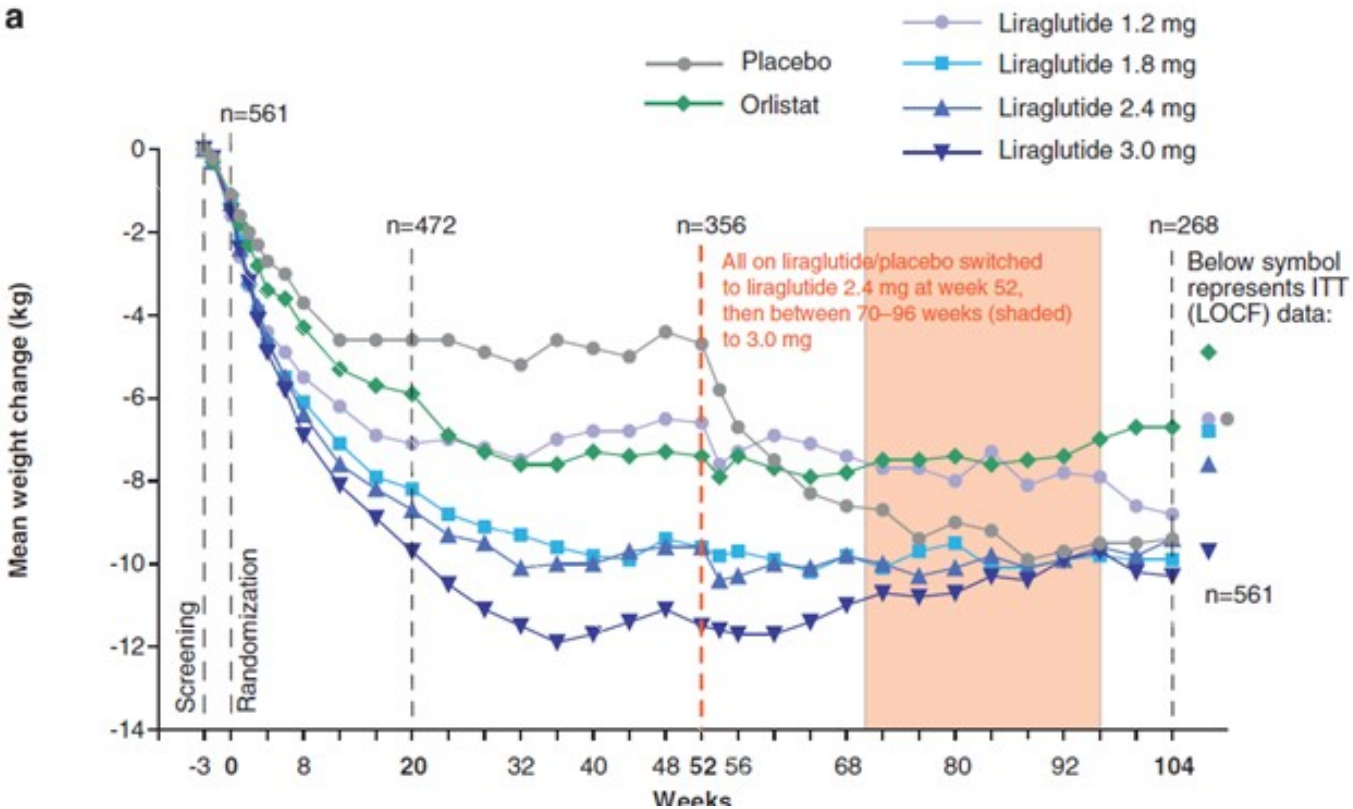
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent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

Liraglutide e rischio cardiovascolare: dal diabete all'obesità

TOPICS

- Rischio cardiovascolare nel diabete e nell'obesità
- Liraglutide: meccanismi d'azione
- Liraglutide e rischio cardiovascolare nel paziente con diabete tipo 2
- Liraglutide nella terapia dell'obesità

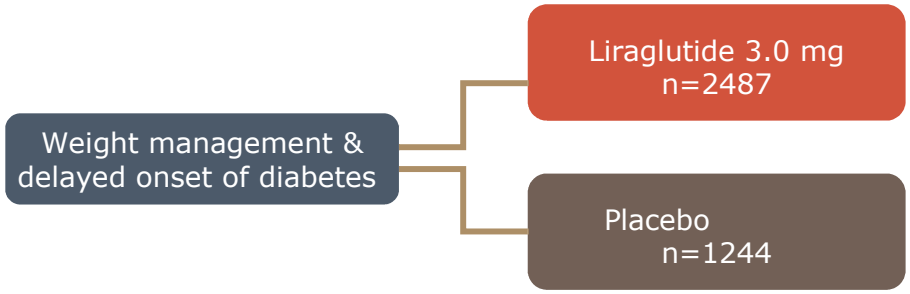
Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide



Astrup A et al. Int J Obesity 2012;36:843-854

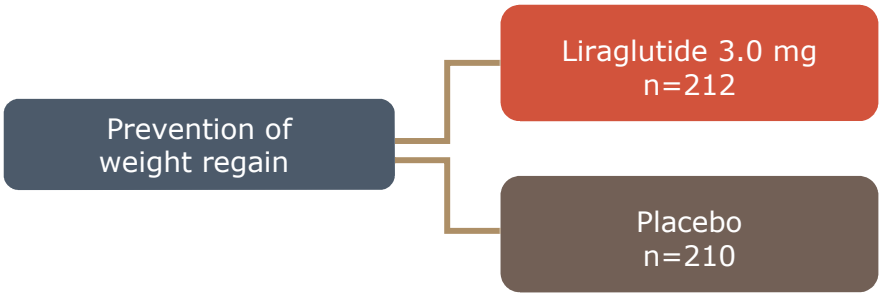
SCALE Phase 3a clinical trial programme

SCALE Obesity and Prediabetes (1839)



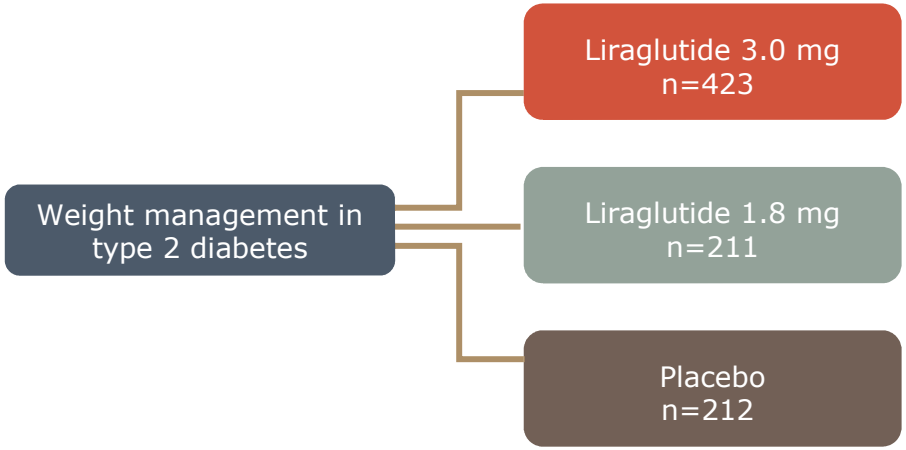
Pi-Sunyer et al. NEJM 2015;373:11-22

SCALE Maintenance (1923)



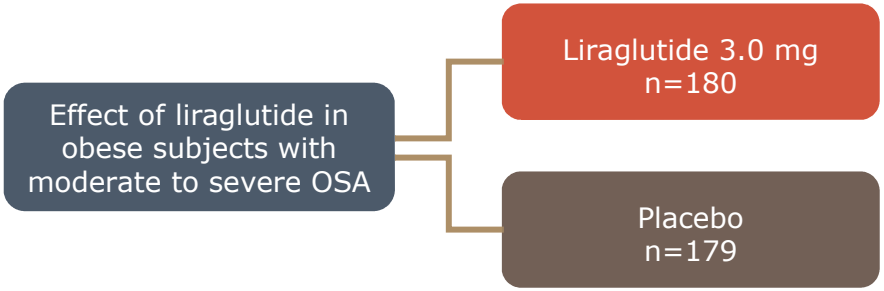
Wadden et al. Int J Obesity 2013;37:1443-51

SCALE Diabetes (1922)



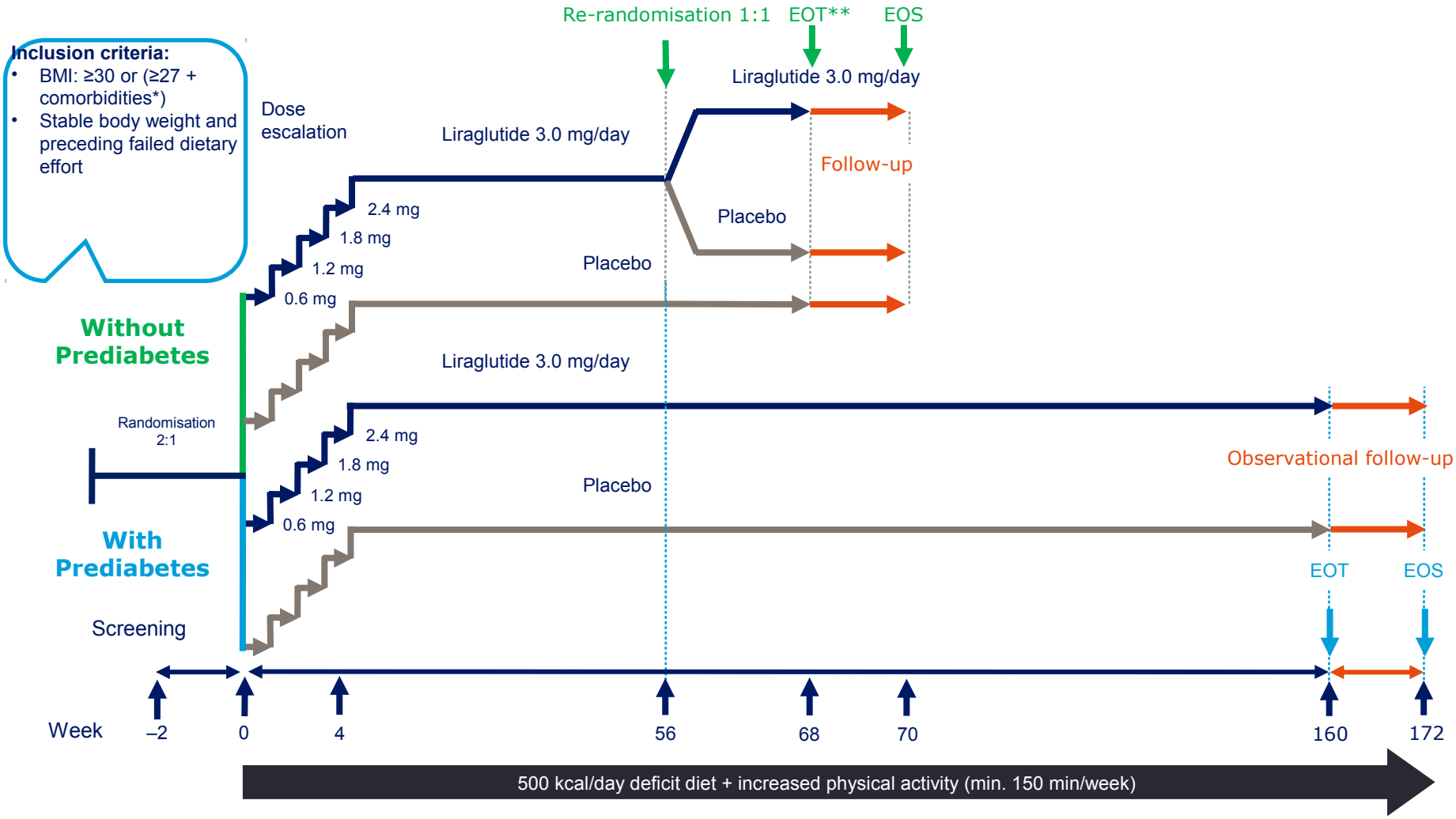
Davies et al. JAMA 2015;314:687-99

SCALE Sleep Apnoea (3970)



Blackman et al. Int J Obesity 2016;40:1310-9

SCALE Obesity and Prediabetes – Trial design



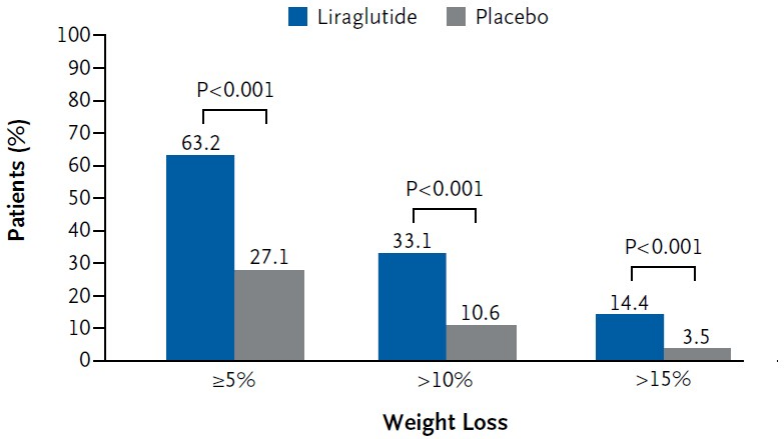
Pi-Sunyer et al. NEJM 2015;373:11-22

SCALE Obesity and Prediabetes

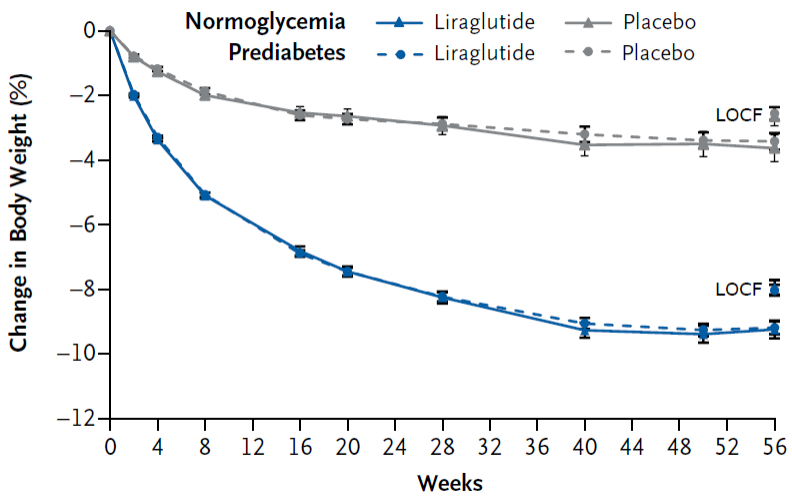
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N=2487)	Placebo (N=1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)

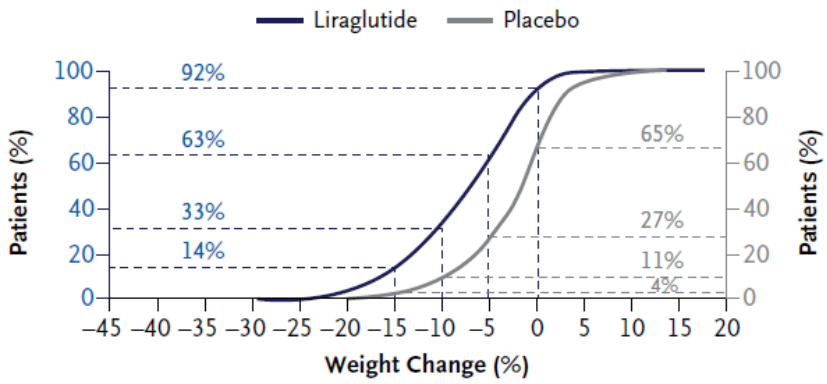
B



A

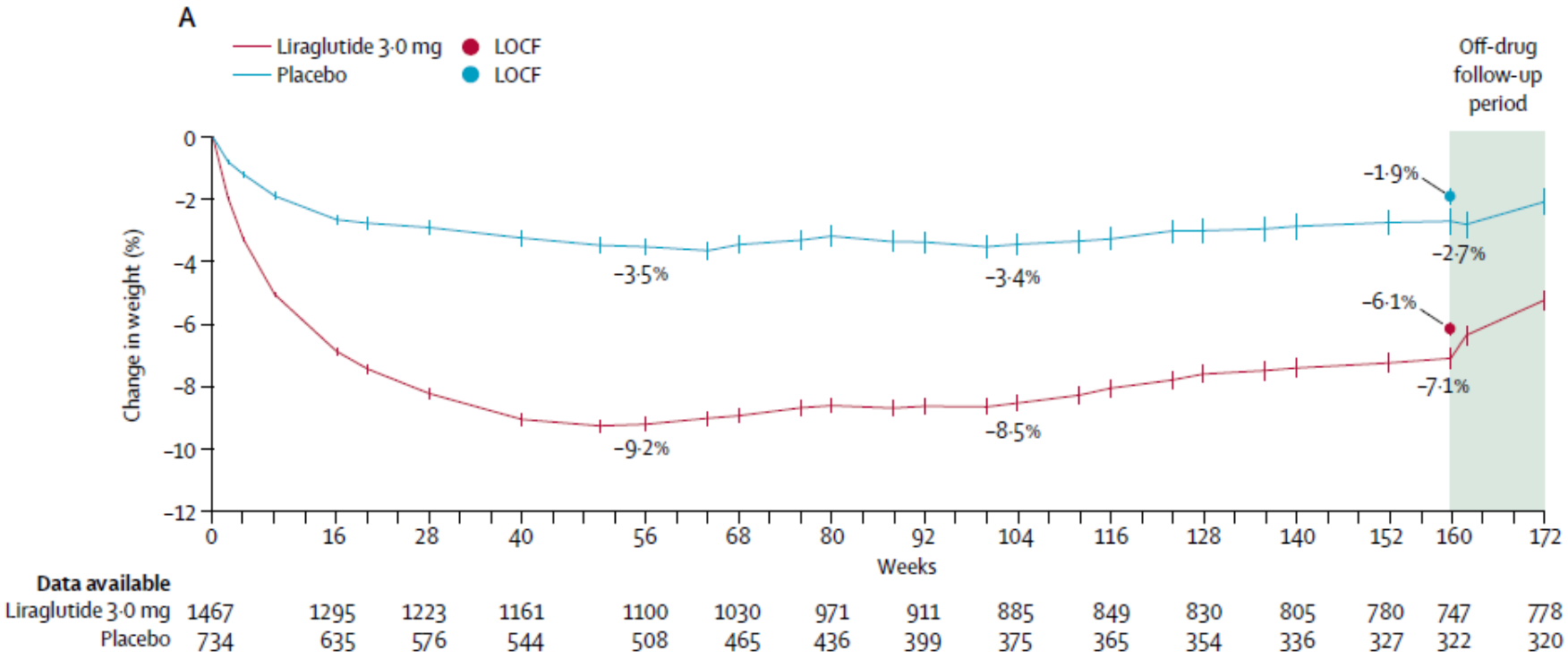


C



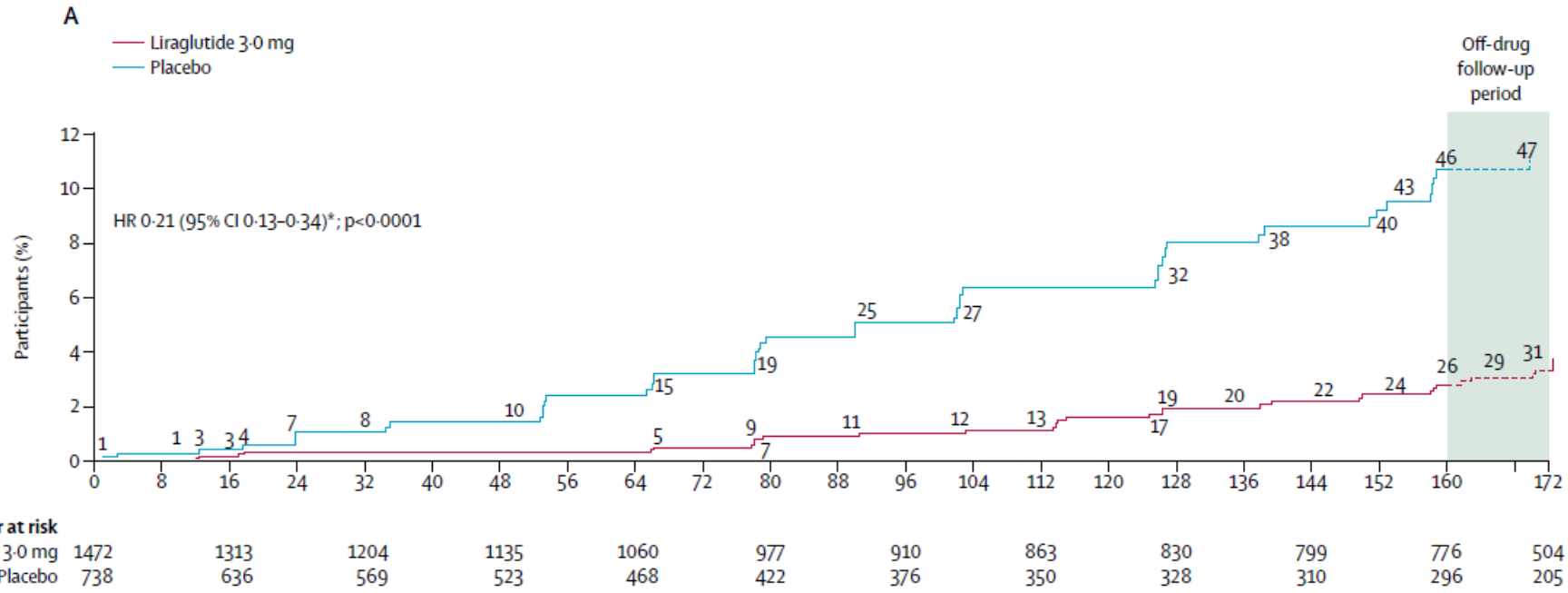
Pi-Sunyer et al. NEJM 2015;373:11-22

3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial



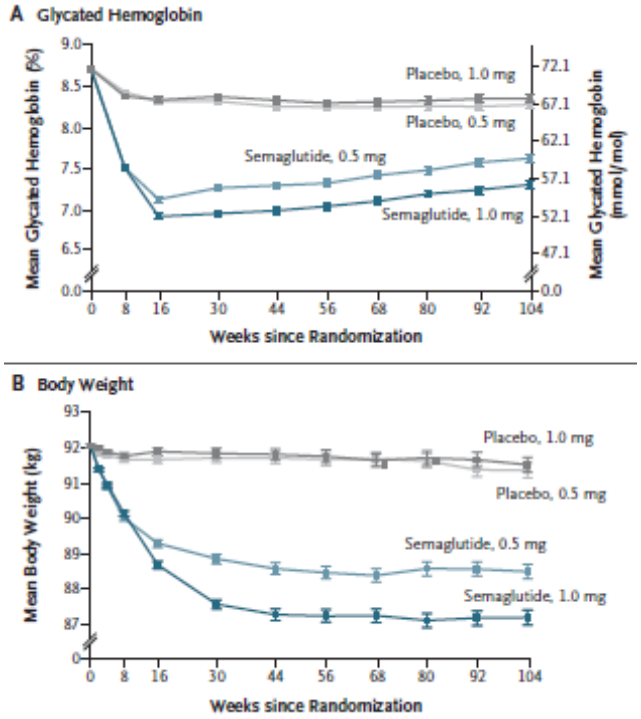
Le Roux C et al. Lancet 2017;389:1399-409.

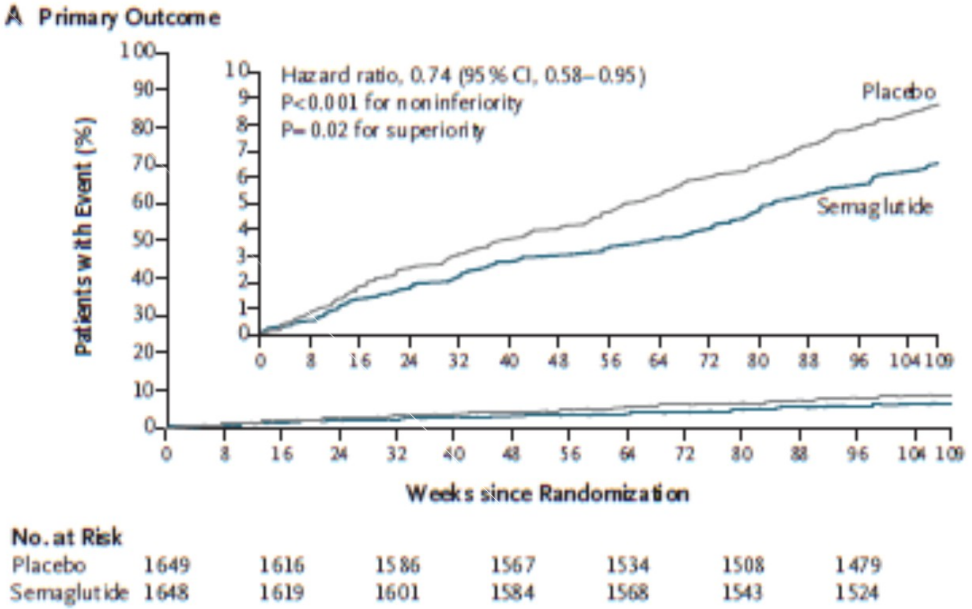
3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial



Le Roux C et al. Lancet 2017;389:1399-409.

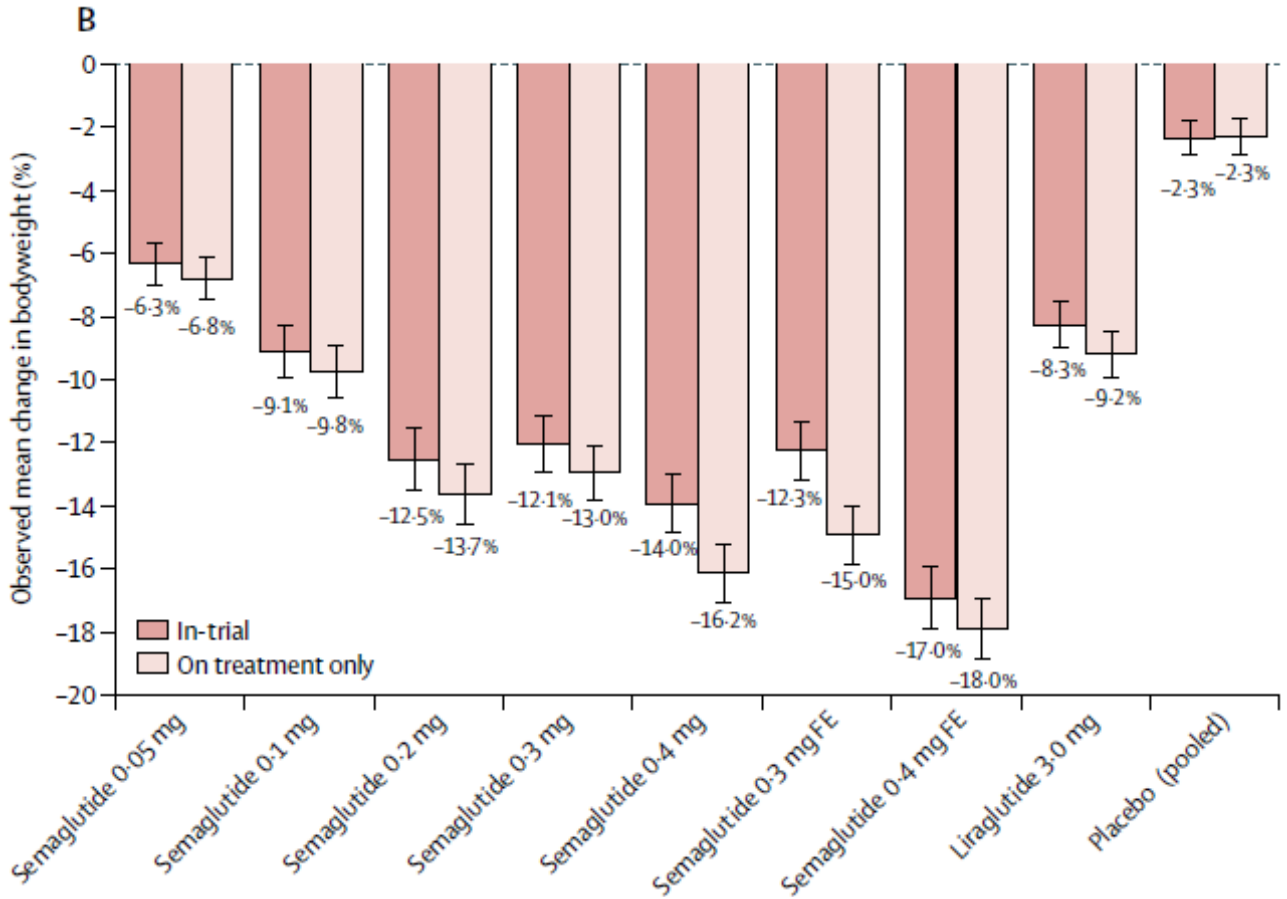
SUSTAIN-6: Semaglutide and cardiovascular outcomes in patients with type 2 diabetes





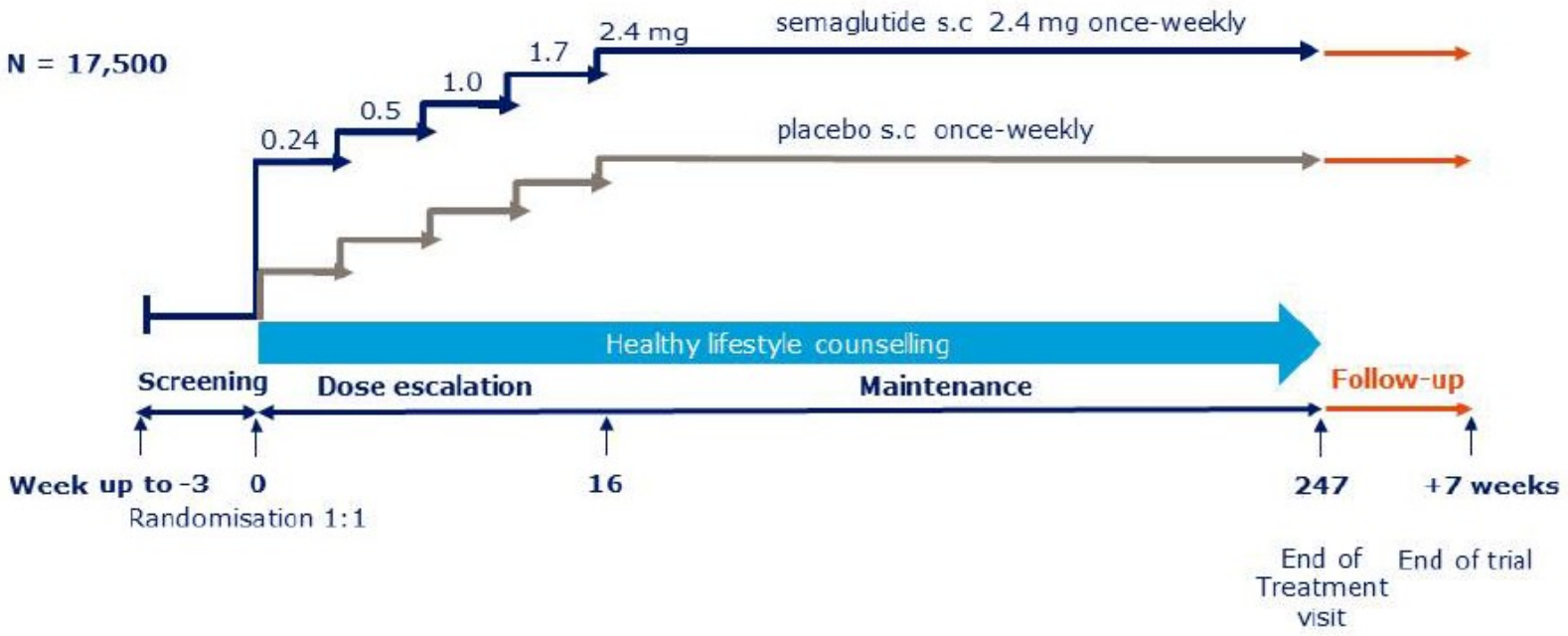
Marso SP et al. N Engl J Med 2016;375:1834

Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial



O'Neil PM et al. Lancet 2018;392:637

SELECT TRIAL



SELECT TRIAL

Major inclusion criteria

- Age ≥ 45 years
- BMI ≥ 27 kg/m^2
- Established CV as evidenced by one of the followings:
  - prior myocardial infarction
  - prior stroke (ischemic or hemorragic stroke)
  - symptomatic peripheral vascular disease

Grazie per l'attenzione !!!

luca.busetto@unipd.it

Luca Busetto

@busetto_luca