

Obesity Academy

February 9 2019

HOW DRUGS MAY HELP FOR OBESITY TREATMENT ?



Campus Gasthuisberg

WHY DIETS OFTEN FAIL ?

Many reasons

Resumption of dietary errors

Reduced basal metabolism

Reduction of fat oxidation

Stimulation of orexigen hormones

High number of adipocytes

Psychosocial stress

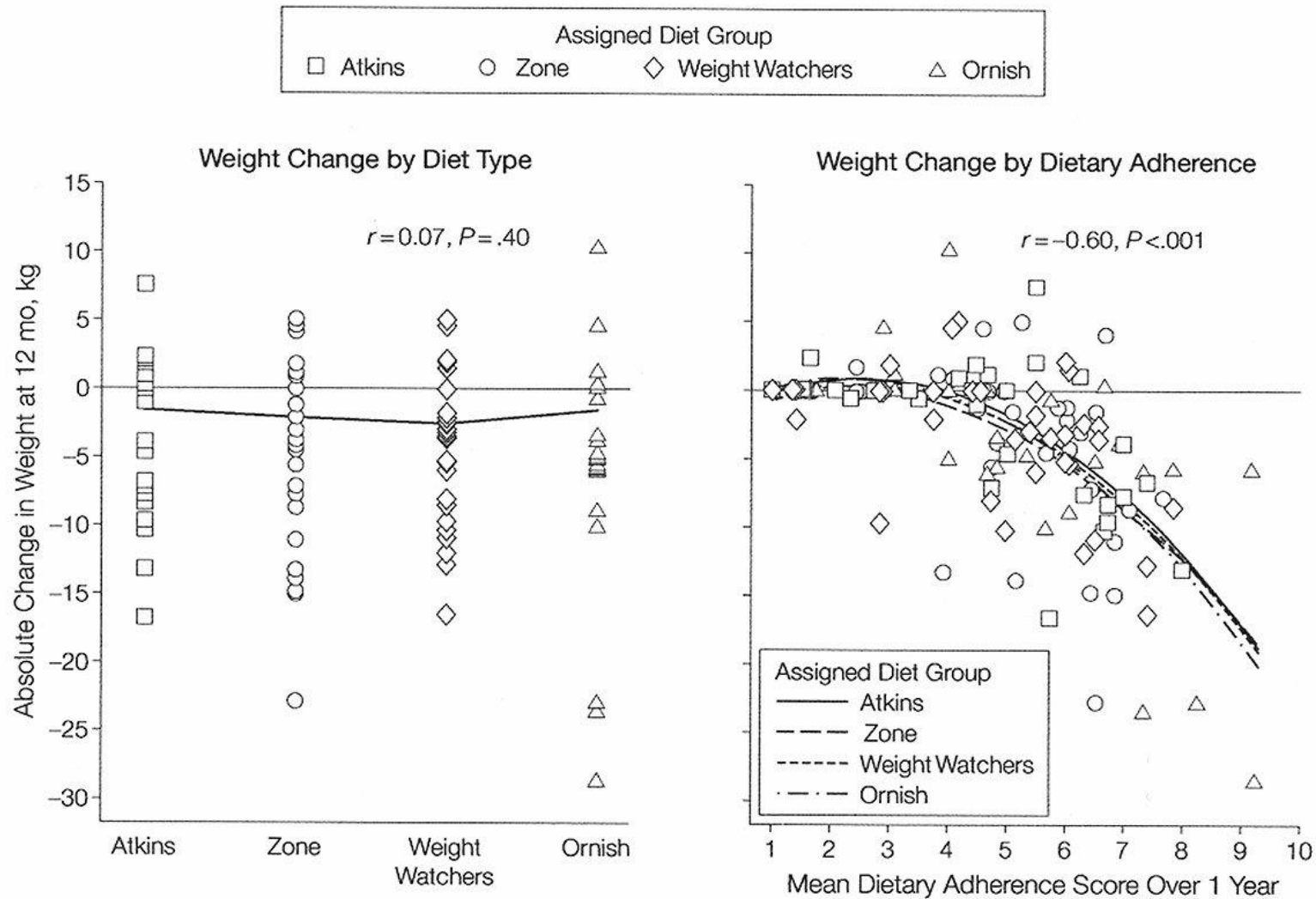
Thrifty phenotype/genotype

Disruption of circadian rhythm

Alterations of the microbiota ?

Endocrine disruptors ?

IS THERE A DIET BETTER THAN ANOTHER ?

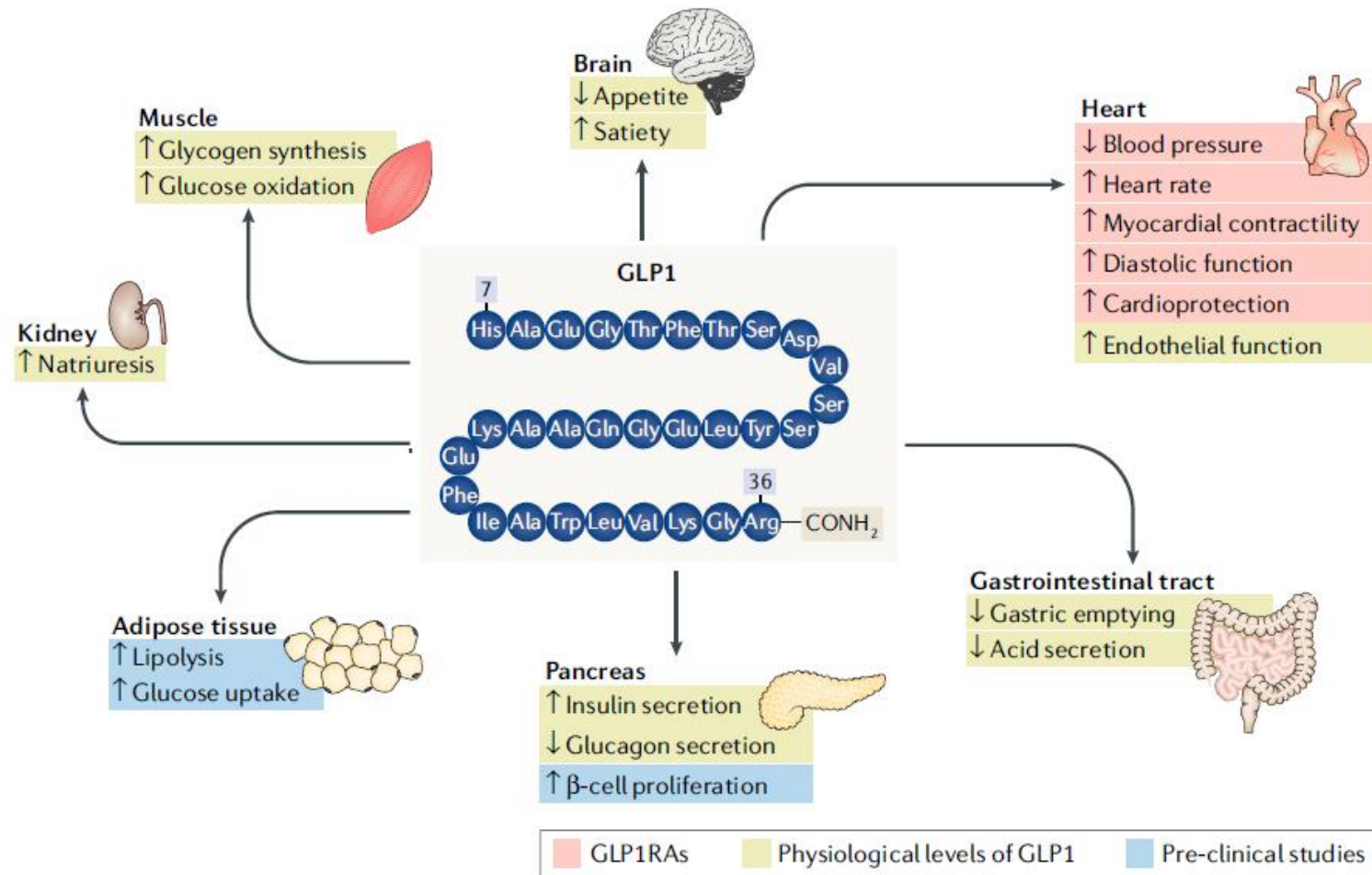


Compliance more important than the nature of the diet....

Dansinger ML et al., 2005

GLP-1

Biological effects of GLP-1



LIRAGLUTIDE (SAXENDA®)

GLP-1 analog

97% homology with native GLP-1

Half-life of 13h

99% bound to albumin

No specific degradation site

No influence of age, gender or ethnicity

Little risk of drug interactions

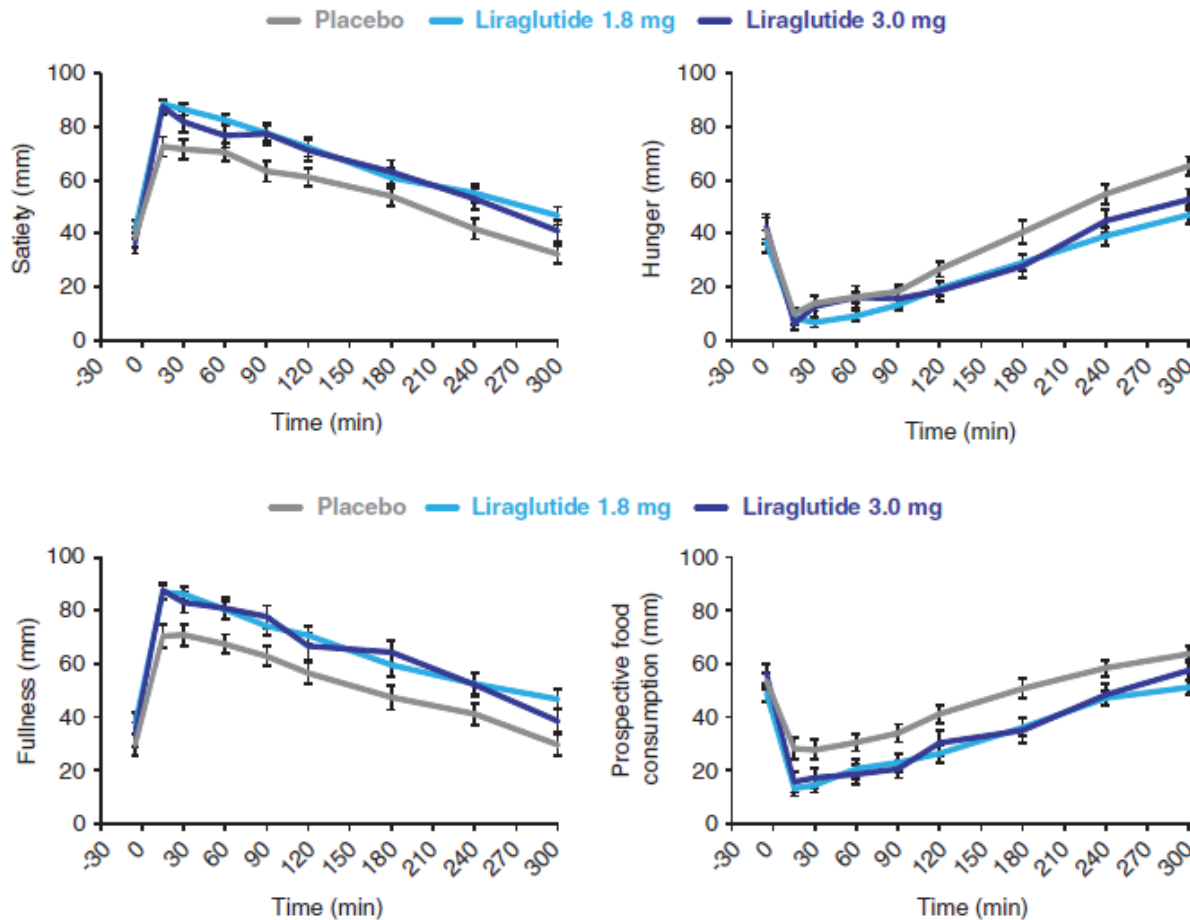
**C-16 fatty acid
(palmitoyl)**



LIRAGLUTIDE (SAXENDA®)

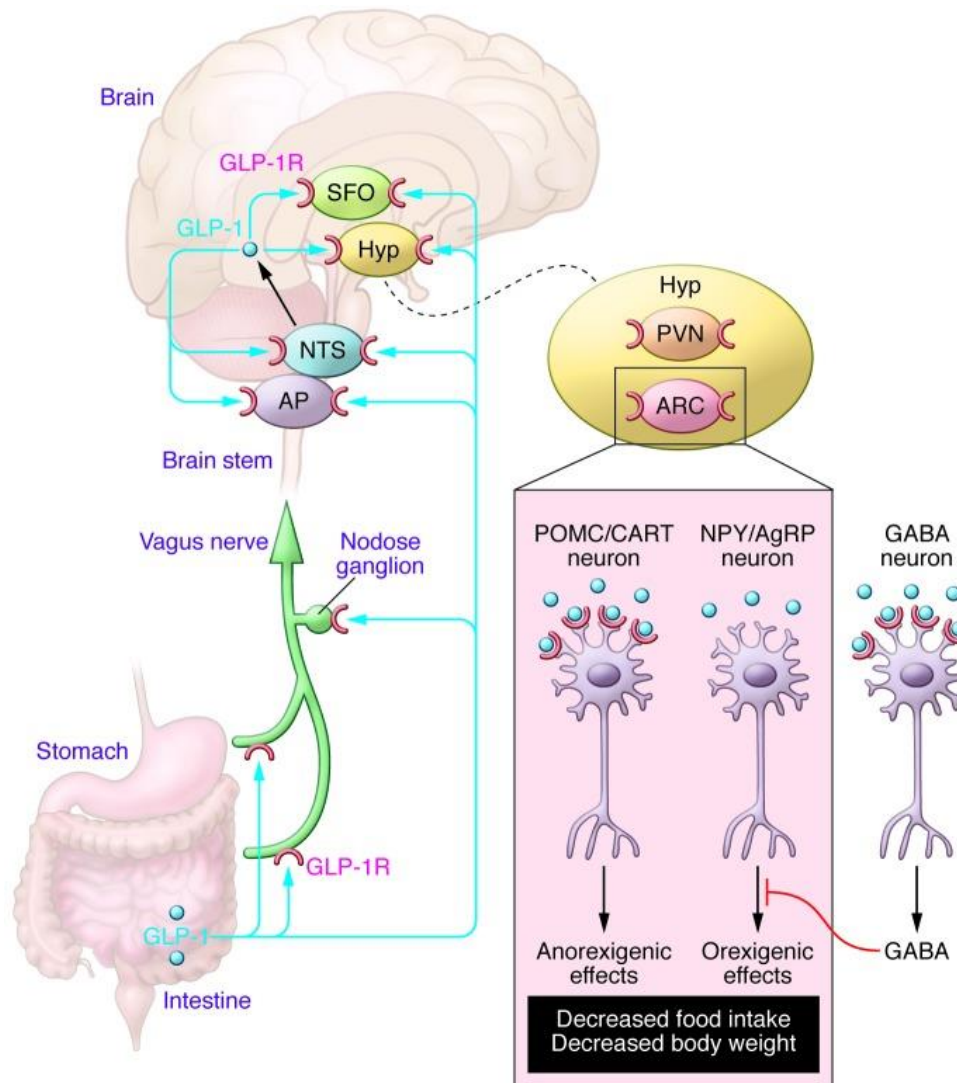
Induction of satiety and attenuation of hunger

Meal test breakfast



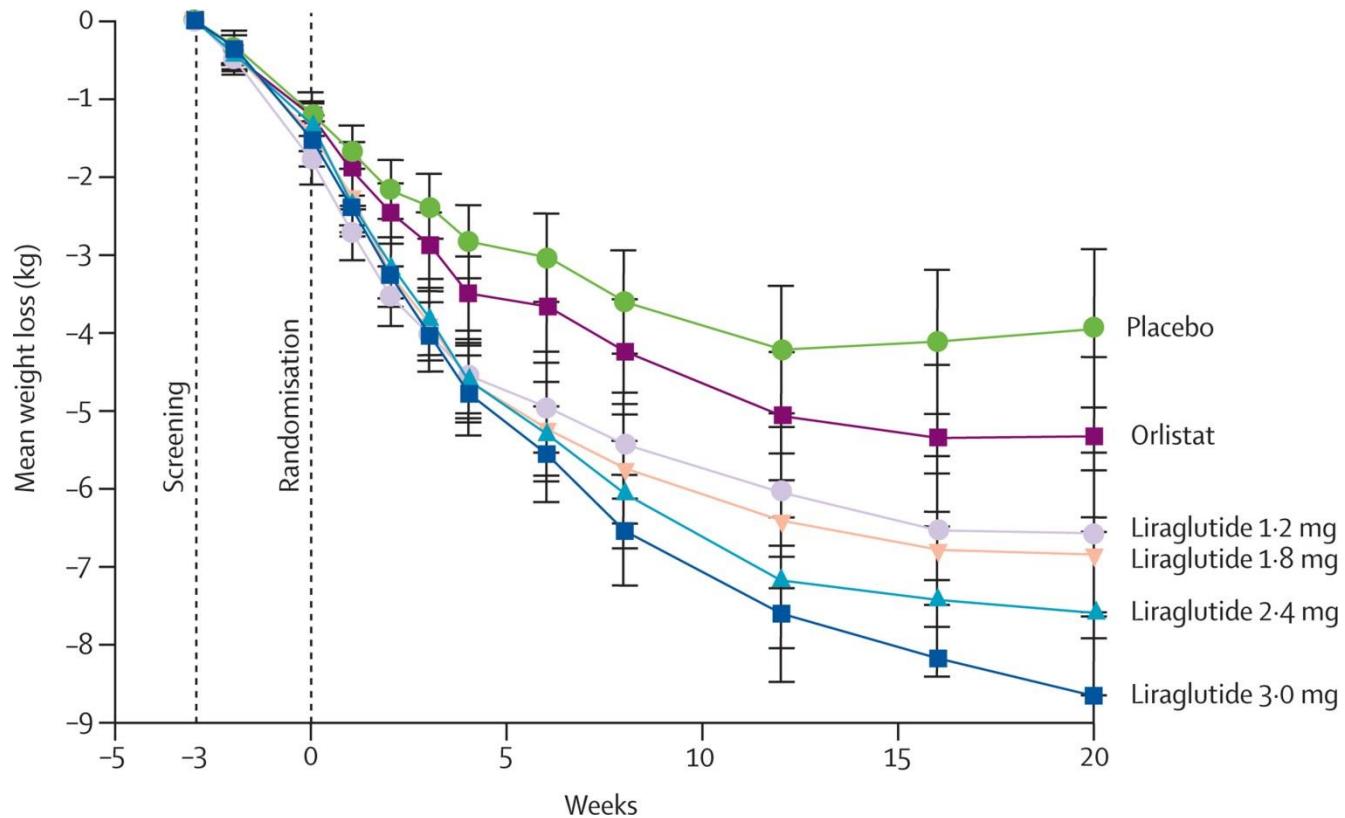
LIRAGLUTIDE (SAXENDA®)

Mechanisms of the anorectic effect



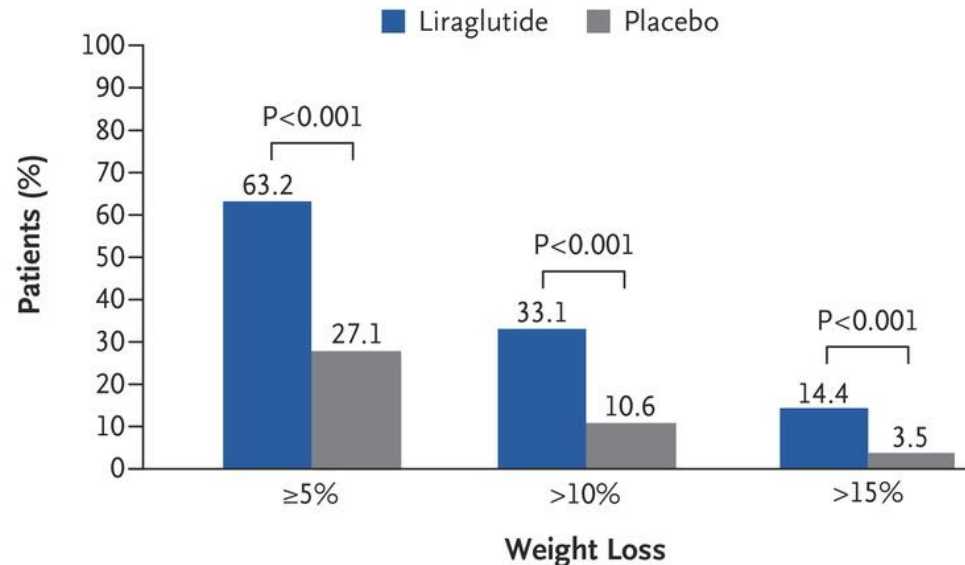
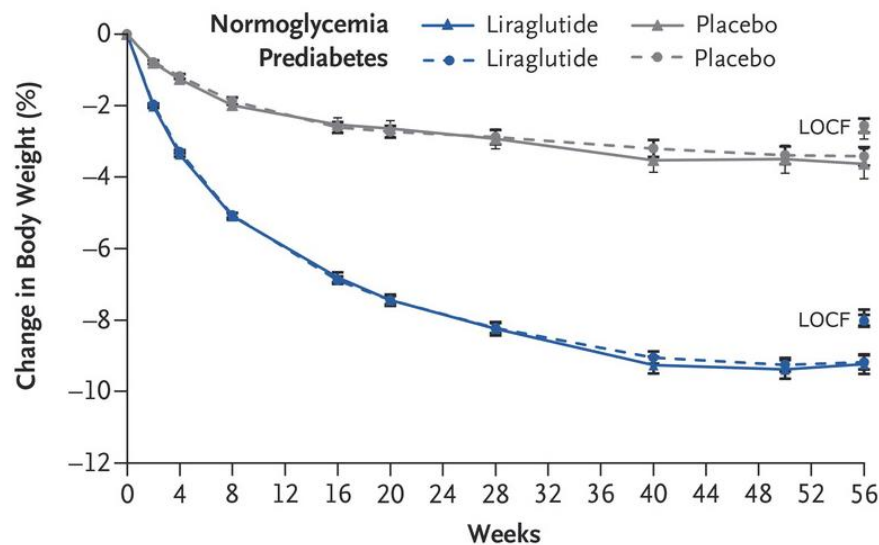
EFFECT OF SAXENDA® ON BODY WEIGHT

Short term study



EFFECT OF SAXENDA® ON BODY WEIGHT

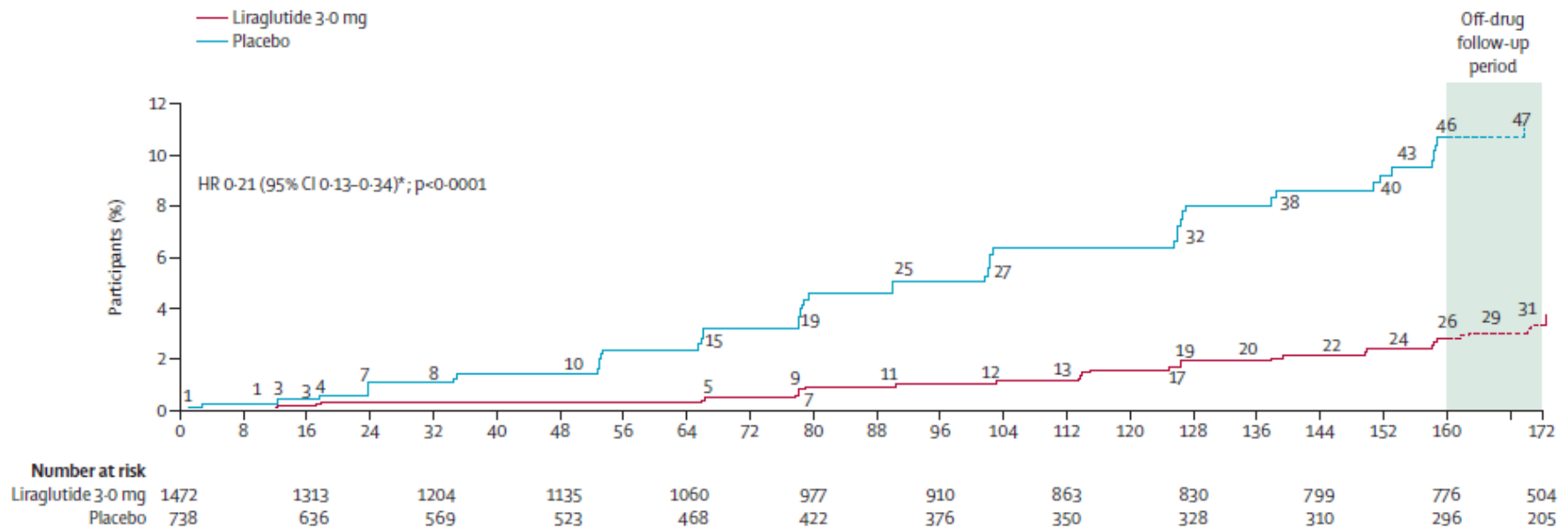
Long-term study SCALE Obesity-Prediabetes



Weight loss 8.4 vs 2.8 kg after 56 weeks

EFFECT ON COMORBIDITIES

Prediabetes mellitus (3 years)



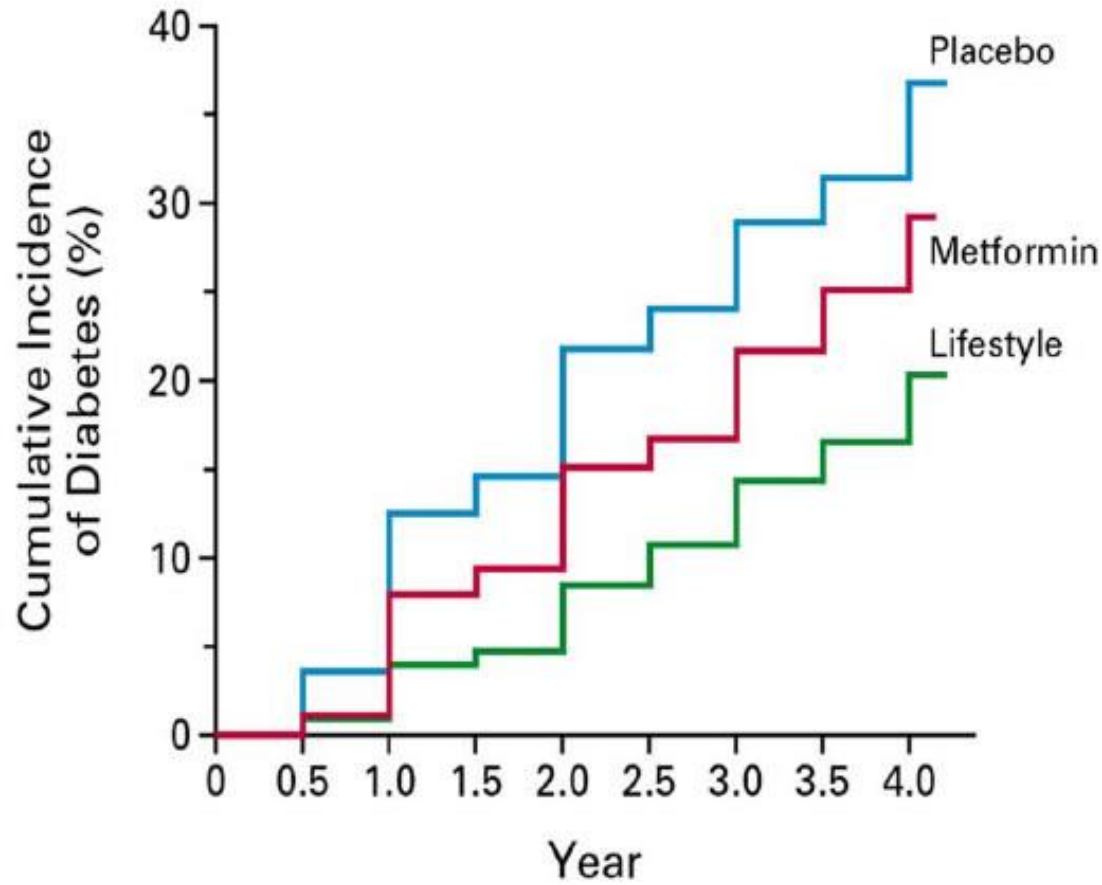
73% reduction in diabetes conversion

2.7x slower conversion

Reduction in the prevalence of prediabetes by 66%

le Roux CW et al., 2017

Modest Weight Loss Prevents Diabetes in Overweight and Obese Persons with Impaired Glucose Tolerance



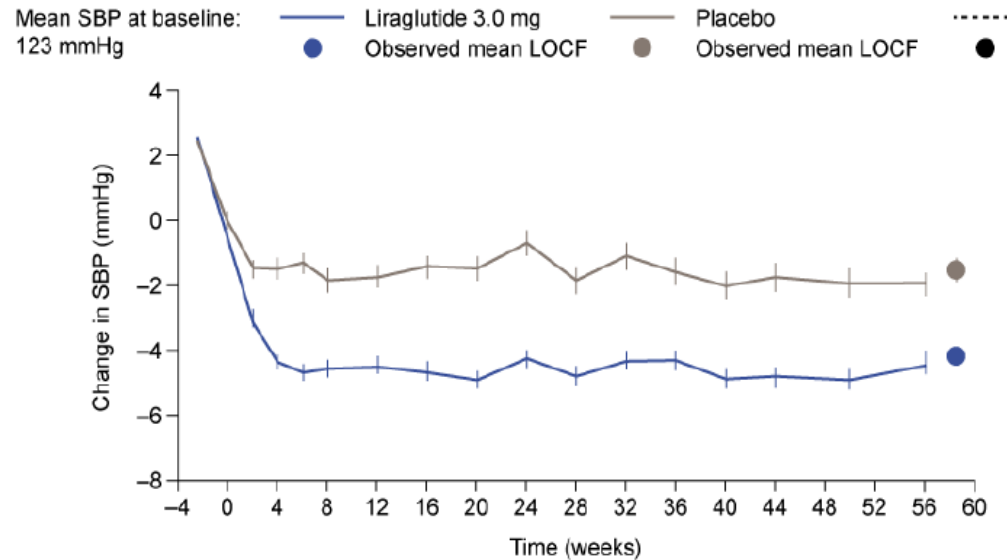
EFFECT ON COMORBIDITIES

Type 2 Diabetes mellitus

End Point	Change From Baseline to Week 56 or Percentage At Week 56			
	Liraglutide			P Value
	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	
Waist circumference, mean (SD), cm ^b	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)	<.001
Body mass index, mean (SD) ^{b,c}	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)	<.001
HbA _{1c} , mean (SD), % change ^b	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)	<.001
No. of individuals achieving HbA _{1c} target, No. % ^d				
<7.0 %	278 (69.2)	130 (66.7)	56 (27.2)	<.001
≤6.5 %	227 (56.5)	89 (45.6)	31 (15.0)	<.001

EFFECT ON COMORBIDITIES

High blood pressure

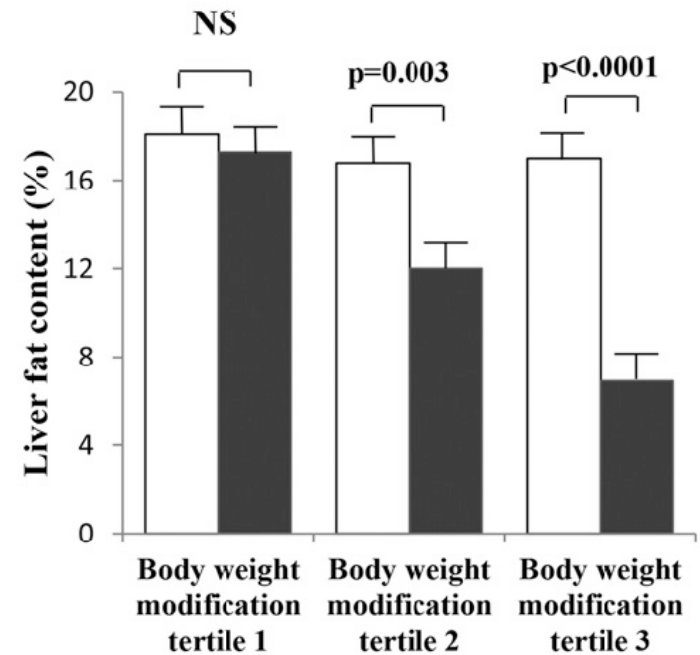
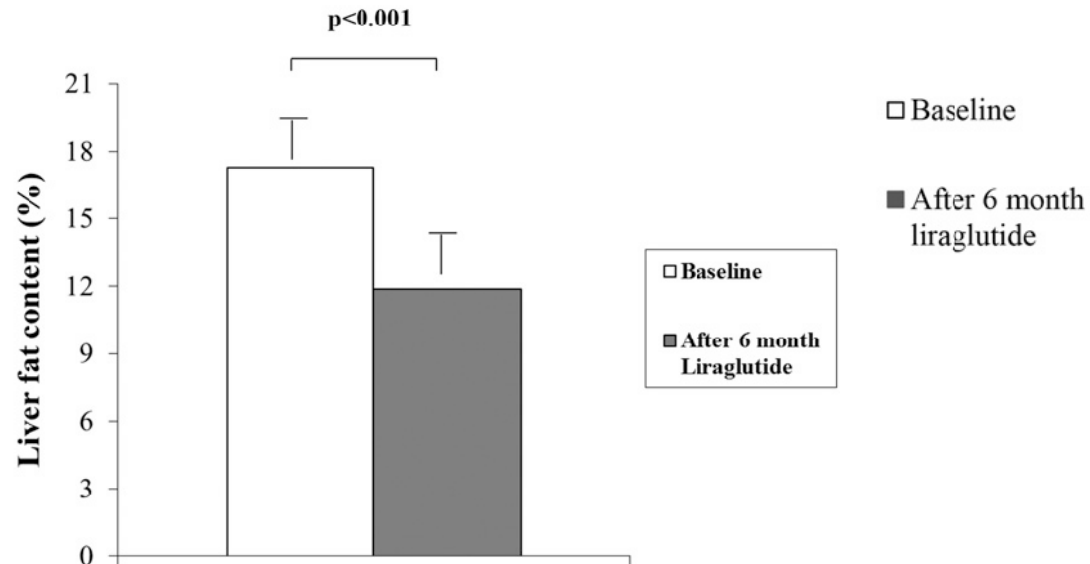


Reduction of the SBP 4.2 vs 1.5 mmHg

Effect of natriuresis

EFFECT ON COMORBIDITIES

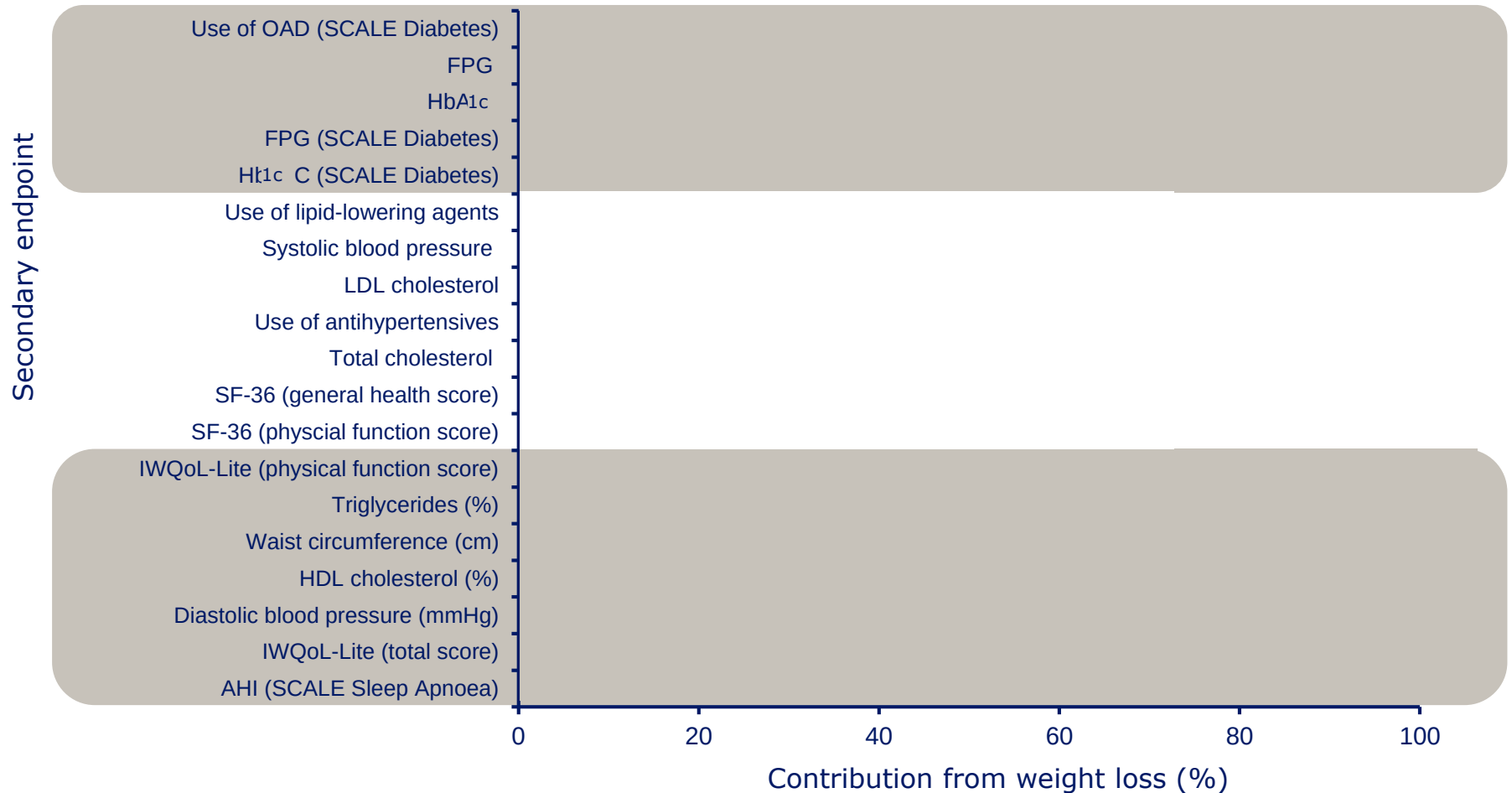
Fatty liver



Effect proportionate to weight loss

Effect not found with insulin

CONTRIBUTION OF WEIGHT LOSS



FAS, LOCF. Data are from SCALE Obesity and Prediabetes (individuals without type 2 diabetes) unless otherwise indicated. AHI, apnoea-hypopnea index; FAS, full analysis set; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IWQoL-Lite, Impact of Weight on Quality of Life-Lite questionnaire; LDL, low-density lipoprotein; OAD, oral antidiabetic drugs; SF-36, 36-item Short-Form health status survey

SIDE EFFECTS

Table 3. Adverse Events and Serious Adverse Events.*

Event	Liraglutide (N = 2481)			Placebo (N = 1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5
Serious adverse events in ≥0.2% of patients	154 (6.2)	194	8.7	62 (5.0)	75	7.0
Cholelithiasis	20 (0.8)	20	0.9	5 (0.4)	5	0.5
Cholecystitis acute	12 (0.5)	12	0.5	0	0	0.0
Osteoarthritis	6 (0.2)	7	0.3	0	0	0.0
Intervertebral disc protrusion	5 (0.2)	5	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	4 (0.2)	4	0.2	0	0	0.0
Cholecystitis	4 (0.2)	4	0.2	0	0	0.0
Breast cancer	4 (0.2)	4	0.2	1 (0.1)	1	0.1
Back pain	2 (0.1)	2	<0.1	2 (0.2)	2	0.2
Uterine leiomyoma	1 (<0.1)	1	<0.1	2 (0.2)	2	0.2
Cellulitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.3
Gastroesophageal reflux disease	0	0	0.0	2 (0.2)	2	0.2
Bronchitis	0	0	0.0	2 (0.2)	2	0.2
Bladder prolapse	0	0	0.0	2 (0.2)	2	0.2
Chest pain	0	0	0.0	3 (0.2)	3	0.3

SCALE

Obesity-Prediabetes



Pi-Sunyer X et al., 2015

SAFETY

Acute pancreatitis

Post-hoc review of LEAD studies

Incidence

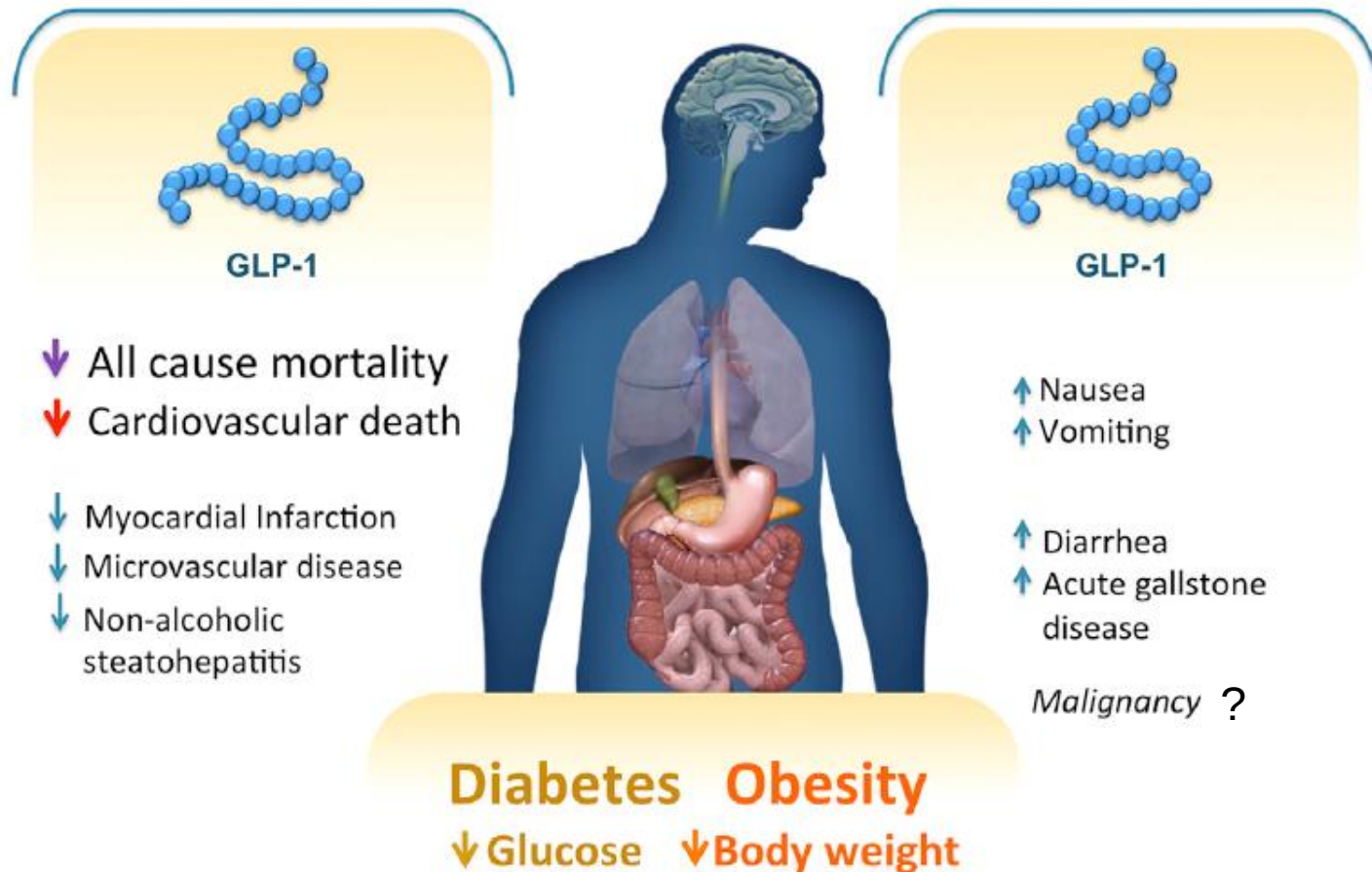
1.6 case / 1000 patient-year exposure (PAE) for liraglutide
0.7 cases / 1000 PAE for comparators

Not all cases meet the diagnostic criteria for pancreatitis

Presence of confounding variables in 75% acute pancreatitis associated with Liraglutide

SAFETY

Major cardiovascular events



CONTRA-INDICATIONS OF SAXENDA®

Pregnancy

History of MEN2 or CMT

Severe gastroparesis

Risk of pancreatitis

(EtOH, known cholelithiasis, history of pancreatitis, hyperTG)

Severe renal insufficiency (GFR <30 ml/min)

Severe hepatic or cardiac insufficiency



INDICATIONS OF SAXENDA®

Obesity $\geq 30 \text{ kg/m}^2$

Overweight $\geq 27 \text{ kg/m}^2$
with dysglycemia, hypertension, dyslipidemia, SAS

In addition
a low-calorie "diet" and
an increase in physical activity

HOW TO USE SAXENDA ?

Obesity grade 1 and 2 (complicated overweight)

Prediabetes

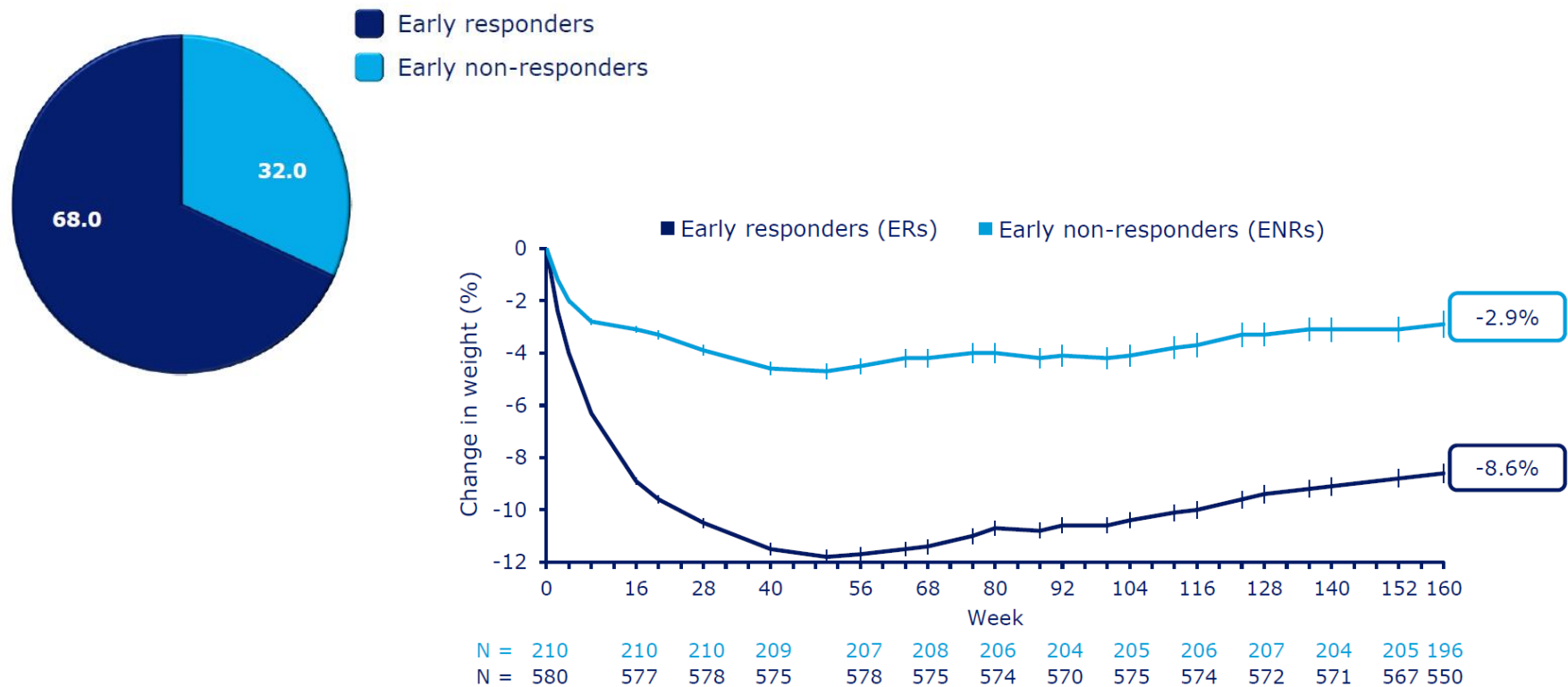
After weight loss $> 5\%$

When a weight loss is a prerequisite for surgery



SELECTION OF THE GOOD RESPONDERS

Weight loss > 5 % in 16 weeks = good responders !



UNANSWERED QUESTIONS

Effect on morbidity and mortality in non-diabetics?

Cost-benefit ratio?

Good answering machines?

Optimal duration of treatment?

Indications of choice?



