ACCADEMIA di
ALTA FORMAZIONE CLINICA
per MEDICI del TERRITORIO

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OBESITA' e MEDICINA TERRITORIALE

elevata prevalenza e trasversalità a molte patologie croniche

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INTRODUZIONE ALL'OBESITA'

elevata prevalenza e trasversalità a molte patologie croniche

Fabio Lucio Albini

Sovrappeso

BMI ≥ 25

Obesità

BMI ≥ 30

Circonferenza addominale

In Europa:

Uomini < 94 cm

Donne < 80 cm

Per valori >94/80 avremo:

Sovrappeso a distribuzione Viscerale (se BMI>25)

Obesità a distribuzione Viscerale (se BMI >30)

Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366(9491):1059-1062.
doi:10.1016/S0140-6736(05)67402-8

Definition and classification of obesity

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

$$BMI = \frac{weight\ (kg)}{height\ (m^2)}$$

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obesity	≥30
Obesity class I	≥30 and <35
Obesity class II	≥35 and <40
Obesity class III	≥40

WHO. Factsheet 311. 2014. http://www.who.int/

L’obesità sta alla base della maggior parte delle patologie cardio-vascolo-metaboliche e di moltissime altre patologie croniche

Obesity is associated with multiple comorbidities and complications

Metabolic, mechanical and mental

Metabolic

Mechanical

Mental

Cancers*

Physical functioning

Depression

Anxiety

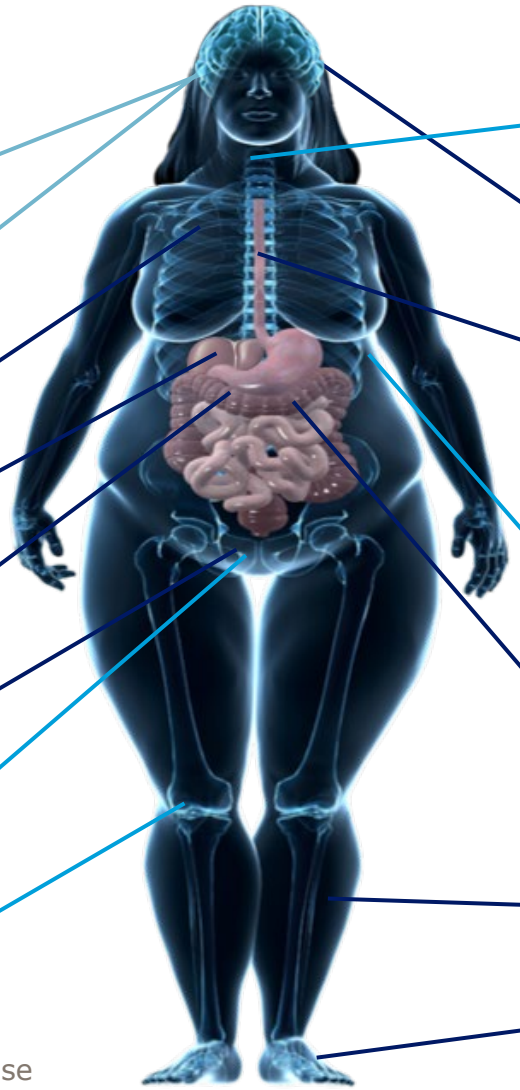
Asthma

NAFLD

Gallstones

Chronic Kidney Disease

Arthrosis



Sleep apnoea

CVD and risk factors
- Stroke
- Dyslipidaemia
- Hypertension
- Coronary artery disease
- Congestive heart failure
- Pulmonary embolism

Chronic Kidney Disease

Type 2 diabetes
Prediabetes

Thrombosis

Gout

CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease
*Including breast, colorectal, endometrial, esophageal, kidney, ovarian, pancreatic and prostate

Adapted from Sharma AM. *Obes Rev*. 2010;11:808-9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic Dis* 2009;6:A48

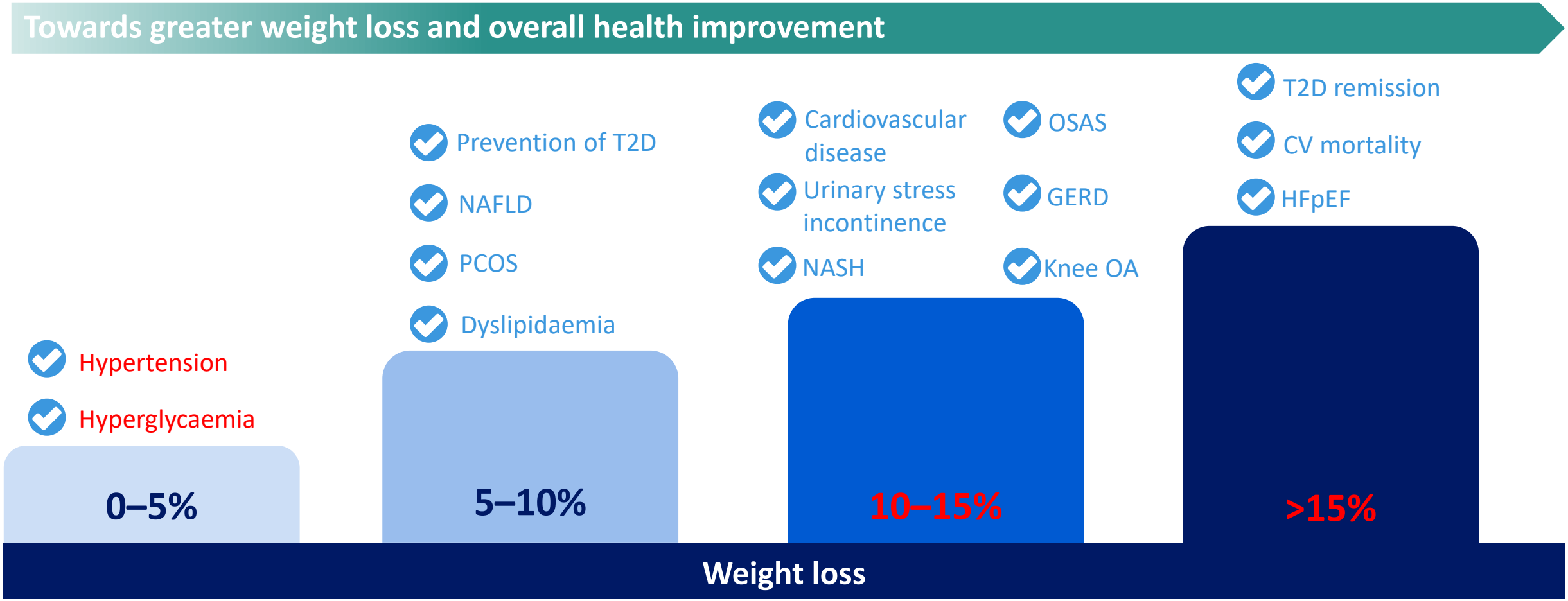
Weight loss may improve obesity related comorbidities

Benefits of 5–10% weight loss

- Reduction in risk of type 2 diabetes[1]
- Reduction in CV mortality[2]
- Improvements in blood lipid profile[3]
- Improvements in blood pressure[4]
- Improvements in severity of obstructive sleep apnoea[5,6]
- Improvements in health-related quality of life[7,8]

1. Knowler *et al*. *N Engl J Med* 2002;346:393–403; 2. Li *et al*. *Lancet Diabetes Endocrinol* 2014;2:474–80; 3. Datillo *et al*. *Am J Clin Nutr* 1992;56:320–8; 4. Wing *et al*. *Diabetes Care* 2011;34:1481–6; 5. Foster *et al*. *Arch Intern Med* 2009;169:1619–26; 6. Kuna *et al*. *Sleep* 2013;36:641–9; 7. Warkentin *et al*. *Obes Rev* 2014;15:169–82; 8. Wright *et al*. *J Health Psychol* 2013;18:574–86

The effect of weight loss on complications



CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides.

Dati Istat 2021

- il 34% della popolazione adulta italiana è sovrappeso
- il 12% è obeso
- **La somma di obesi+sovrappeso italiani è del 46%!**
- La maggior prevalenza è al Sud, la minore al Nord e in Toscana e Lazio
- La prevalenza degli obesi è in lenta ma costante crescita: da 8,5% (2002) a 12% (2021)

PREMESSE SULL'OBESITA'

a) OBESITA' ORMAI RICONOSCIUTA VERA MALATTIA (cronica-recidivante-progressiva)
b) COSTITUISCE UN GRAVE PROBLEMA DI SALUTE (individuale e pubblica)
c) NECESSARIA AZIONE IMMEDIATA DI PREVENZIONE/CONTROLLO DI QUESTA PANDEMIA

Se osserviamo la situazione globale di questi nostri pazienti quasi sempre rileviamo :

1. una ostinata negazione del problema-peso, oppure…

2. una confusione di attività, operate dai pazienti stessi (rimedi miracolistici, strane diete, buste sostitutive pasto), intervallate da vari interventi sanitari scollegati fra loro (biologi nutrizionisti-medici dietologi-endocrinologi-bariatrici)

3. Mancata presenza e supervisione del medico del territorio (in primis il medico di famiglia) come punto di appoggio e sintesi nel percorso clinico long-life che questi pazienti meriterebbero.

* L’intervento da parte del Medico territoriale (eventualmente supportato da un team dietologo/psicologo) sui soggetti in incremento ponderale dovrebbe essere particolarmente precoce ed incisivo, coinvolgendo anche l’ambito familiare. Questo proprio per la posizione privilegiata nel poter sorvegliare ed essere rapidamente proattivo con qs pz.

* E’ anche fondamentale conoscere ed eventualmente introdurre specifici farmaci che hanno dimostrato significativa efficacia clinica nella riduzione del peso in eccesso e nel mantenimento di quello già perso.

*Evitare che un sovrappeso divenga obeso o far perdere del peso ad un obeso, significa facilitare una dignitosa qualità della vita e una fondamentale "protezione" dalle svariate patologie-correlate che provocano drammatici eventi fatali o morbilità invalidanti

*le strategie comportamentali sono importanti nella gestione dei pz sovrappeso/obesi per rendere efficaci gli interventi su alimentazione e attività fisica, ed integrarli all'eventuale supporto di terapia farmacologica specifica.

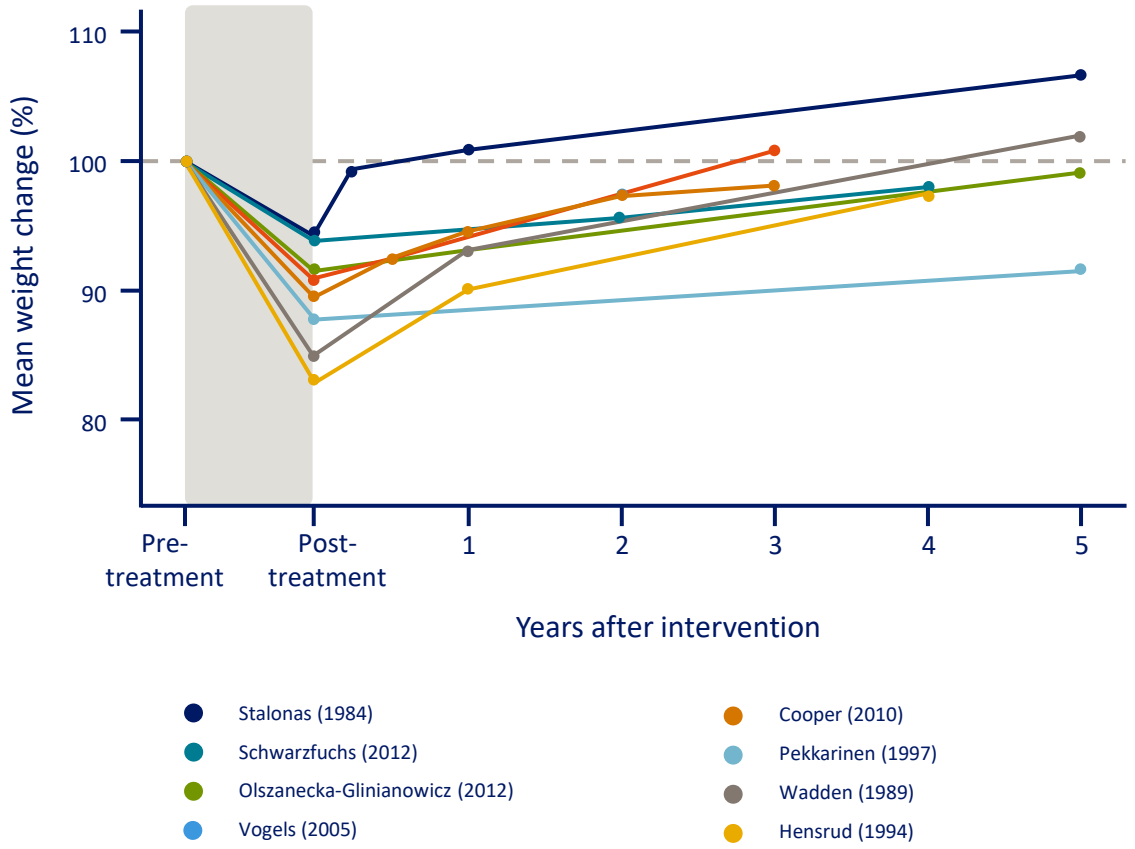
Con uno sguardo sempre rivolto alla loro riproducibilità nel setting della Medicina Territoriale

OBESITA' COME MALATTIA CRONICA-PROGRESSIVA-RECIDIVANTE

- **IL PESO TENDE LENTAMENTE A CRESCERE DOPO I 40 aa**
- **IL RITMO DI INCREMENTO DEL PESO E' DI 1 Kg OGNI 4 ANNI**
- **LA PERDITA DI PESO SCATENA AUTOMATICAMENTE DEI COMPLESSI MECCANISMI ADATTATIVI CHE FAVORISCONO IL RECUPERO DEL PESO PERSO**
- **NON ESISTE A TUTT'OGGI UN METODO, UN FARMACO, UNA PROCEDURA CHE TRASFORMI STABILMENTE IL METABOLISMO DI UN «DIMAGRITO» NEL METABOLISMO DI UN «MAGRO»**

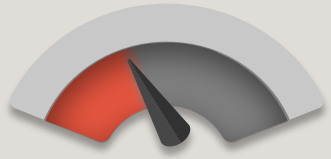
Long-term weight loss is challenging

Maintenance of weight loss



Metabolic adaptation following weight loss

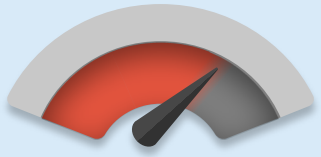
Weight loss



Adaptations that resist weight loss:

- **Hormone levels**
  - ↓ satiety hormones
  - ↑ hunger hormones
- **Metabolism**
  - ↓ energy expenditure

Weight regain



E’ PERTANTO NECESSARIO…

- …Sorveglianza da parte del Medico territoriale sui soggetti a rischio di incrementare di peso
- …Azione già nella fase di sovrappeso con interventi ripetuti di minimal advise e supporto dietologico/psicologico + prescrizione di attività fisica aerobica personalizzata e costante

Per ogni anno «perso senza far nulla» si aggiunge stabilmente più massa grassa,
: un perverso meccanismo di perpetuo auto-incremento del peso.

VIGILANZA E PROATTIVITA' NELLE FASI PIU' A RISCHIO PER AUMENTO DI PESO

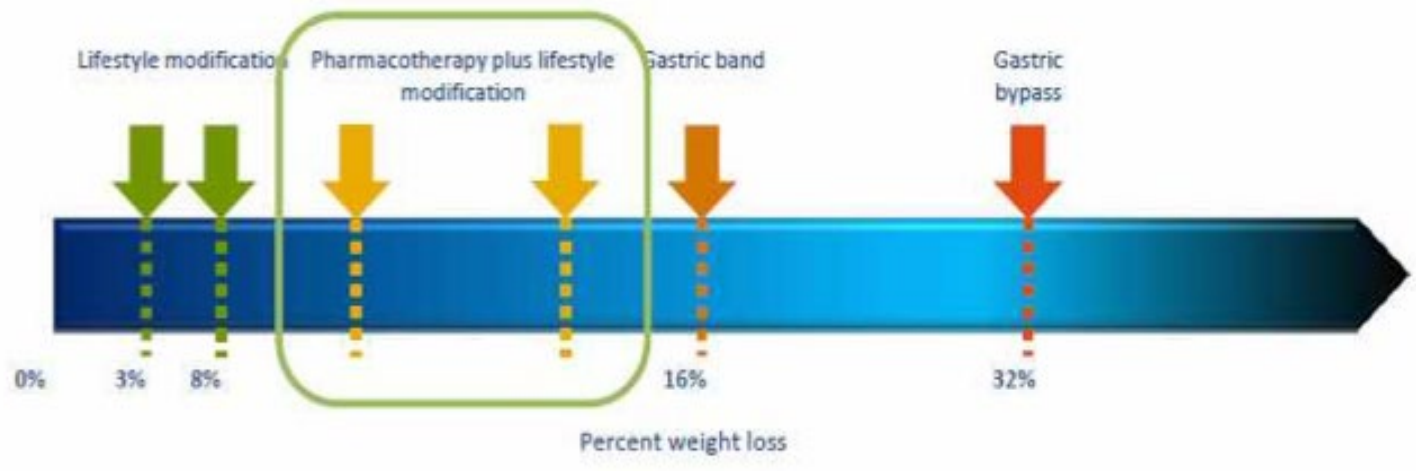
- Infanzia avanzata/preadolescenza (soprattutto in presenza di familiarità diretta x obesità o classe socio-economica meno agiata)
- Periodo peri-menopausale; sospensione attività lavorativa e/o sessuale negli uomini
- Sospensione di una Consolidata Dipendenza (Fumo in primis ma anche droghe), come anche la Sospensione Improvvisa di uno Sport attivo o di una attività aerobica costante
- Insorgenza di Stato Depressivo; inizio di terapie Anti-Psicotiche

I periodi sopraelencati rappresentano, nell'arco della vita, una possibilità maggiore di sviluppare sovrappeso e obesità. Vanno pertanto sorvegliati con attenzione, pre-allertando il paziente del rischio ed eventualmente iniziando a intervenire decisamente sugli stili di vita

DRAFT LG_ISS 2022 (Istituto Superiore Sanità) 2

Sebbene le modifiche dello stile di vita siano alla base degli interventi di prevenzione e trattamento delle malattie metaboliche (1), è ormai chiaro che la loro applicabilità ha molteplici limiti. In particolare, i loro effetti sul peso sono transitori (2-6). La terapia dell'obesità dovrebbe tenere conto del fatto che tutti gli approcci basati sul cambiamento dello stile di vita risultano fallimentari nel breve-medio periodo, e che quindi ad esso vanno precocemente associati trattamenti che possano essere proseguiti nel tempo (come accade per tutte le malattie croniche: ipertensione arteriosa, ipercolesterolemia, diabete mellito).
E' verificabile l'ipotesi che dopo 12 mesi dall'inizio di un intervento per la perdita del peso, la terapia farmacologica (in add-on alla dietoterapia + attività fisica) sia significativamente più efficace nel mantenimento del calo ponderale rispetto alle sole strategie terapeutiche non farmacologiche

TERAPIA FARMACOLOGICA



OBIETTIVI TERAPEUTICI

1. **Perdita di peso**
2. **Mantenimento del peso e prevenzione del nuovo aumento di peso**
3. **Fornire più rapidamente benefici clinici concreti (riduzione rischio DM, malattie CV, miglioramento qualità di vita)**

- ***I farmaci agiscono attraverso meccanismi biologici e adattamento ormonale per indurre riduzione di peso***

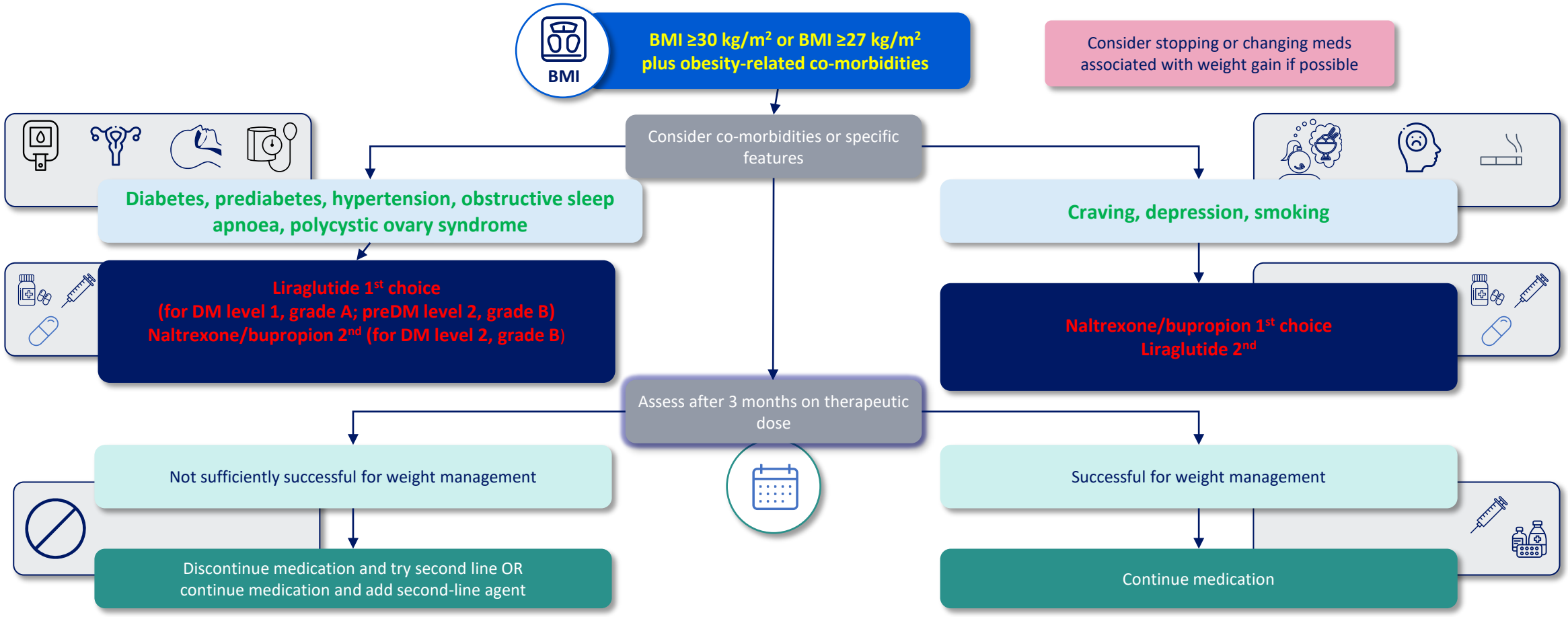
Stepped approach to obesity management

	BMI 25–26.9 kg/m²	BMI 27–29.9 kg/m²	BMI 30–34.9 kg/m²	BMI 35–39.9 kg/m²	BMI ≥40 kg/m²
Surgery 			When optimal medical and behavioural management has been insufficient	**With adiposity-related complications**	+
Pharmacotherapy 		**With adiposity-related complications**	+	+	+
Behavioural modification 	+	+	+	+	+
	All individuals, regardless of body size or composition, benefit from a healthy, well-balanced eating pattern and regular physical activity				

BMI, body mass index.

Wharton S et al. CMAJ 2020;192:E875–91.

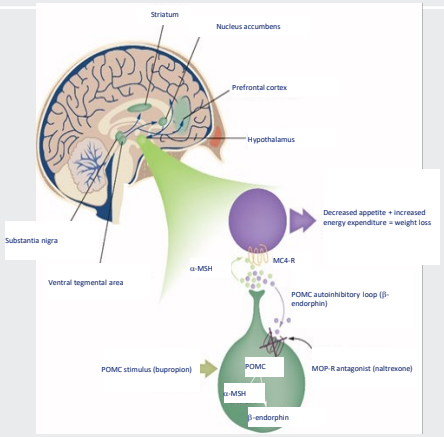
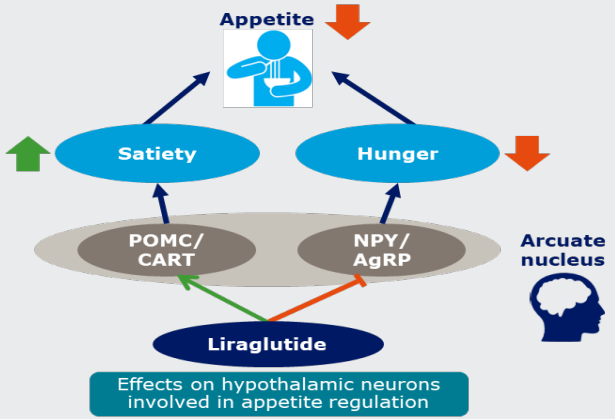
Choice of obesity pharmacotherapy



BMI, body mass index; DM, diabetes mellitus

Pedersen SD et al. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy in Obesity Management. Available from: https://obesitycanada.ca/guidelines/pharmacotherap y. Accessed on 9 August 2020

Pharmacological options for weight management

	Naltrexone/ bupropion	Liraglutide 3.0 mg
Status	US: 9/2014 EU: 3/2015	US: 12/2014 EU: 3/2015
MOA	 **POMC** • Satiety signal • Increased firing leads to weight loss • Activated by bupropion **β-endorphin** • Released with α-MSH • Inhibits POMC firing • Effect blocked by naltrexone	
Dosing	Twice daily, oral	Daily injection
Indications	Adjunct to reduced-calorie diet and increased physical activity for chronic weight management in a) obesity BMI≥30 kg/m^2 or b) overweight BMI≥27+≥1 kg/m^2 comorbidity	

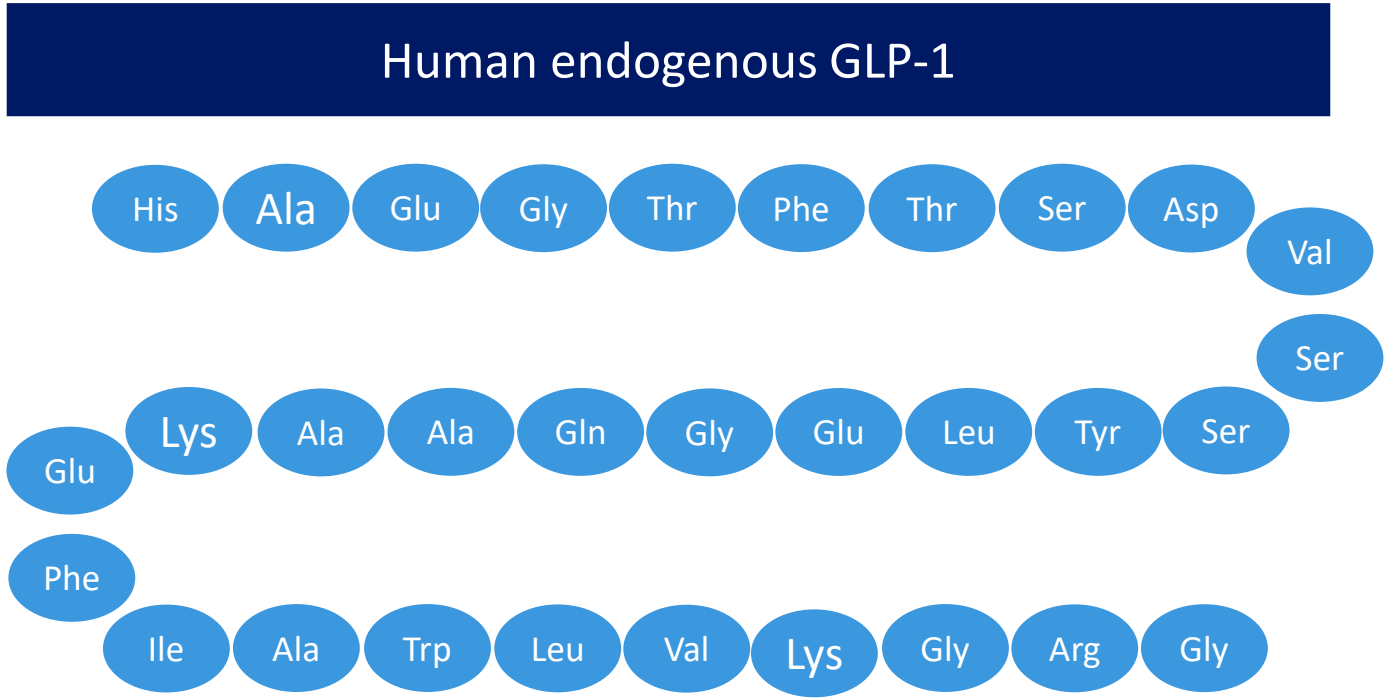
The trial design, duration and baseline characteristics of the participants differ between the trial, hence it may not be a direct comparison

BMI, body mass index; CART,cocaine- and amphetamine-regulated transcript; FFA, free fatty acid; MG, monoglycerides; MOA, mechanism of action; POMC, proopiomelanocortin; NPY/AgRP; neuropeptide Y/Agouti-Related Peptide TG,triglyceride

EMA. EMA Medicines. Available from: http://www.ema.europa.eu/ [accessed 10 March 2020]; FDA. FDA Drugs. Available from: http://www.fda.gov/Drugs/default.htm [accessed 10 March 2020]

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

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life

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

GLP-1RAs have multifactorial effects

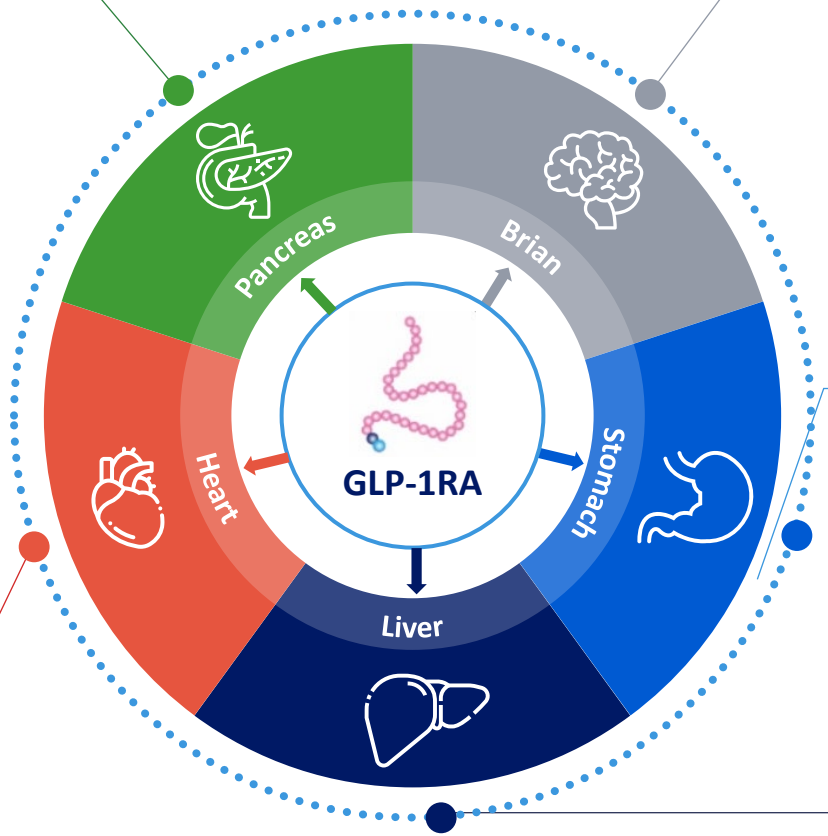
Pharmacological effects

Pancreas

- ↑ Beta-cell function[1]
- ↑ Beta-cell apoptosis[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]

Liver

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

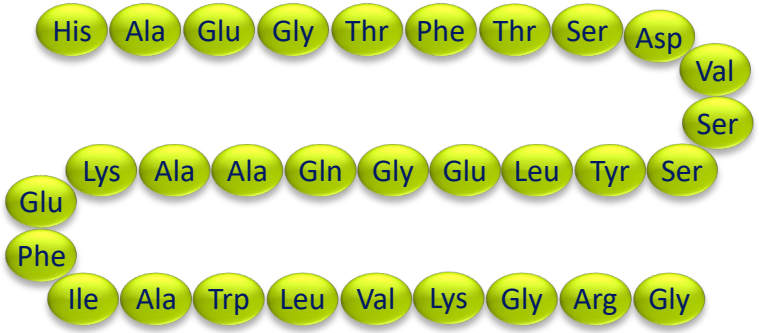
Heart

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

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

Adapted from Campbell & Drucker. Cell Metab 2013;17:819–37; Pratley & Gilbert. Rev Diabet Stud 2008;5:73–94. Full reference list in slide notes; Mehta et al. Obes Sci Pract. 2017;3(1):3-14

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



Human endogenous GLP-1

$t_{½}$ = ~2 mins

C-16 fatty acid (palmitoyl)

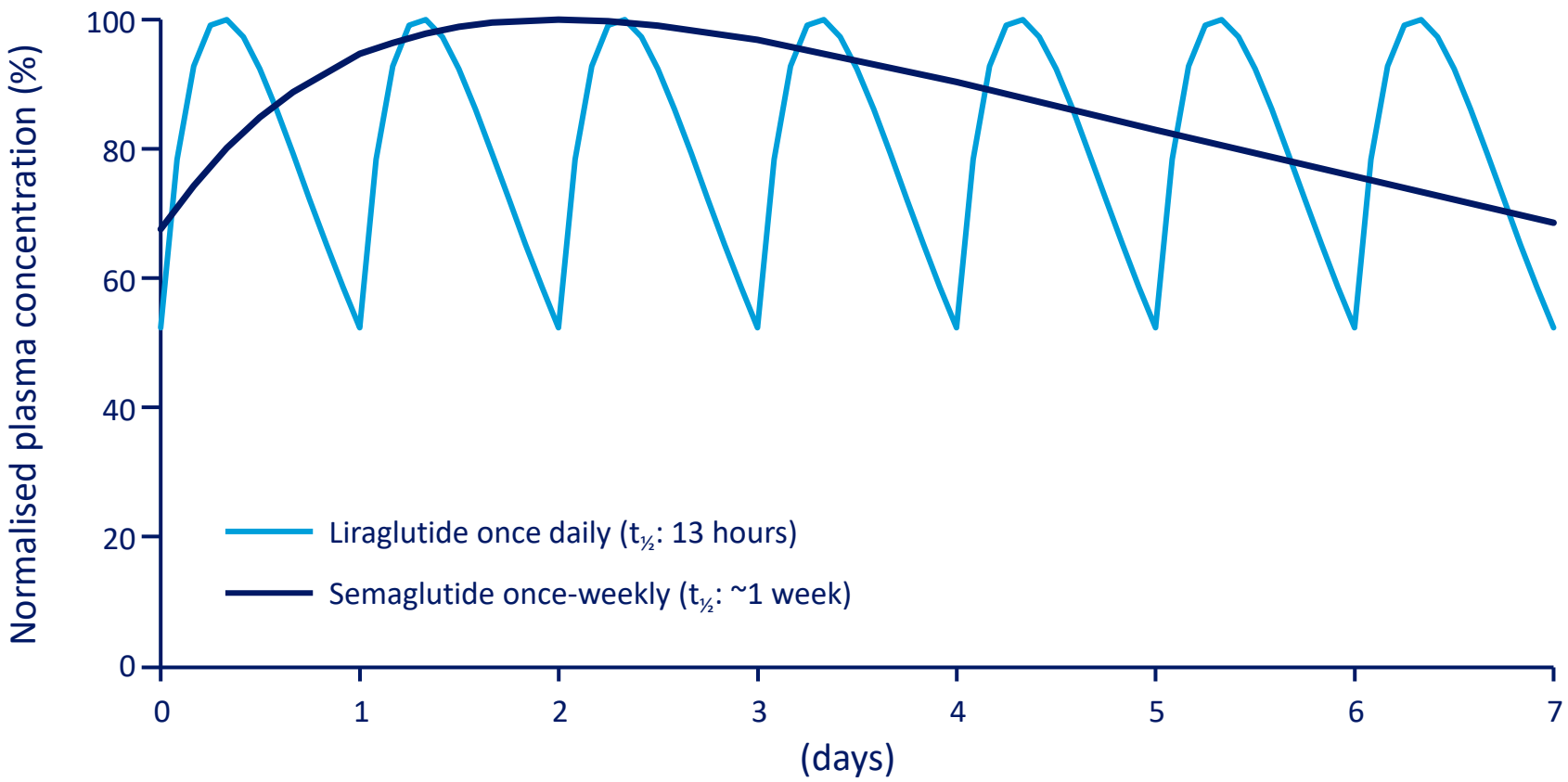
Liraglutide

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)

DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide-1; PK, pharmacokinetics
Knudsen et al. J Med Chem 2000;43:1664–1669; Degn et al. Diabetes 2004;53:1187–1194

plasma levels with liraglutide OD

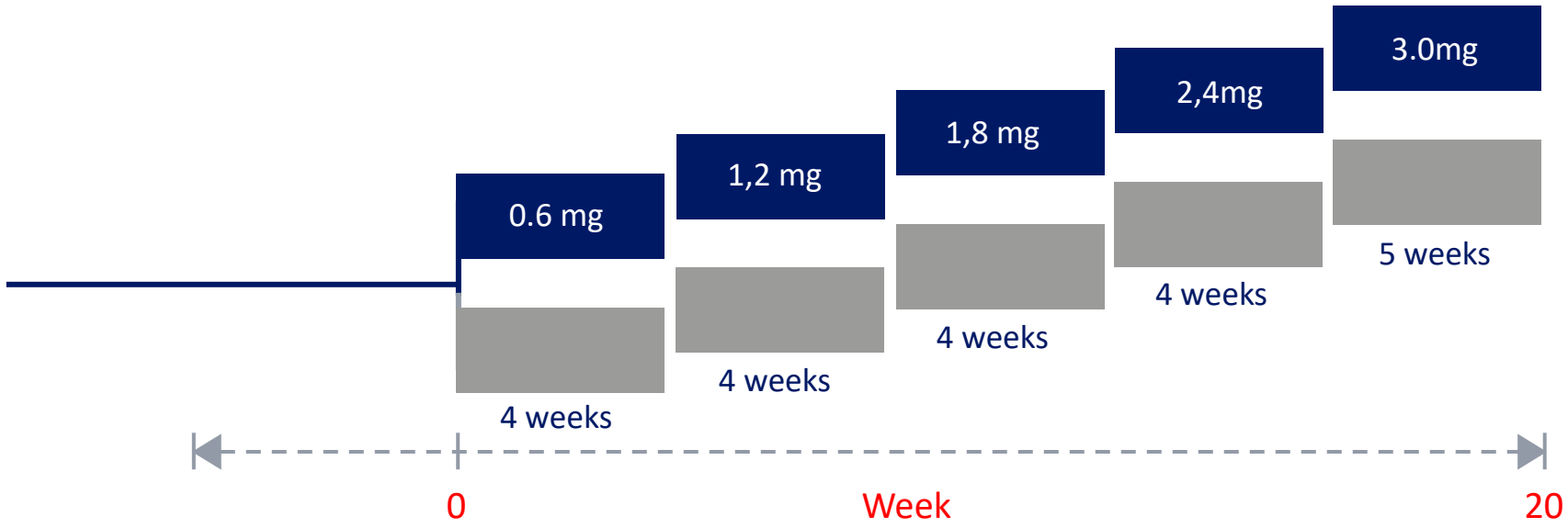


Profiles were based on simulated modelling. Liraglutide is the only GLP-1RA that is approved by the US FDA and EMA for use in overweight/obese participants without T2D. It is dosed once daily.
EMA, European Medicines Agency; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; t½, half life.
Elbrønd et al. Diabetes Care 2002;25:1398–404; Marbury et al. Clin Pharmacokinet 2017;56:1381–90; Novo Nordisk. Data on file.

SOMMINISTRAZIONE DI LIRAGLUTIDE

Una volta al giorno S.C con incrementi ogni 4 settimane:
dalla dose iniziale di 0,6mg/die alla dose ottimale di mantenimento di 3mg/die

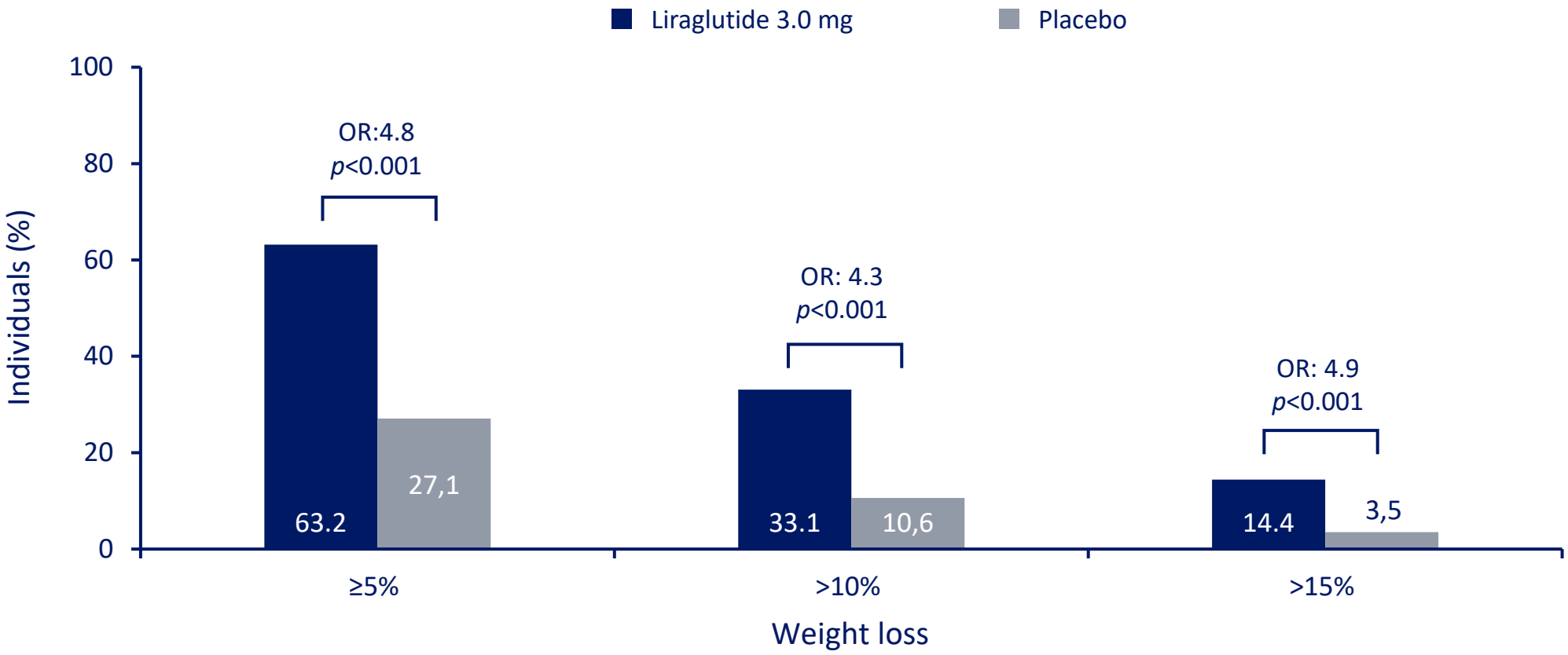
NB: la dose massima giornaliera di Liraglutide per la terapia del Diabete è di 1,8 mg/die !



Categorical weight loss

SCALE Obesity and Prediabetes: At week 56

Mean baseline weight: 106.2 kg

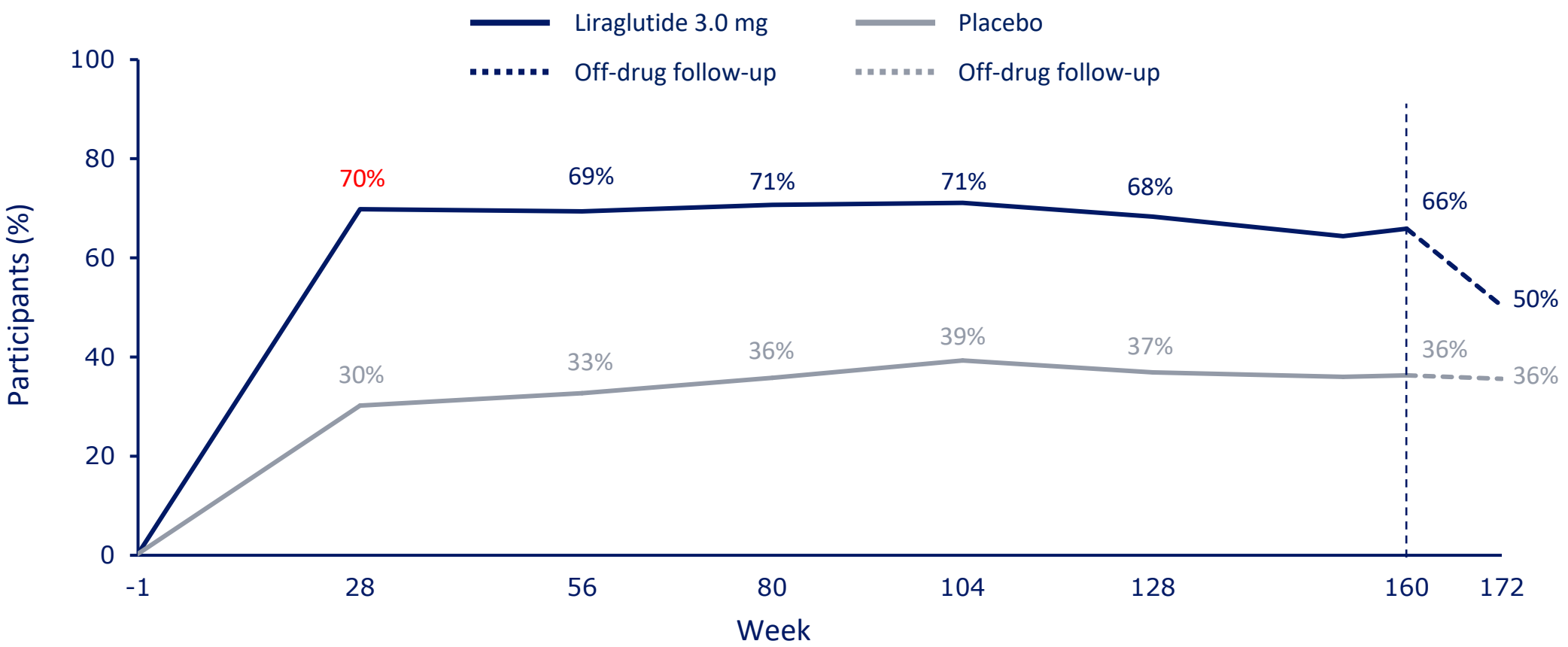


Data are observed means for the full analysis set (with LOCF) and the odds ratios (OR) shown are from a logistic regression analysis (the analysis for achieving 15% weight loss was performed post hoc). LOCF, last observation carried forward; OR, odds ratio

Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Regression to normoglycaemia over time

SCALE Obesity and Prediabetes: 0-172 weeks



Full analysis set, last observation carried forward. Statistical analysis is logistic regression (OR with 95% CI). Normoglycaemia is defined as fasting plasma glucose <100 mg/dL (<5.6 mmol/L) and/or 2-hour post-challenge glucose <140 mg/dL (<7.8 mmol/L) and/or HbA1c <5.7%. Data measured at OGTT visits.
CI, confidence interval; NNT, number needed to treat; OR, estimated odds ratio
le Roux et al. Lancet 2017;389:1399–409

Liraglutide causes large and Rapid Epicardial Fat reduction

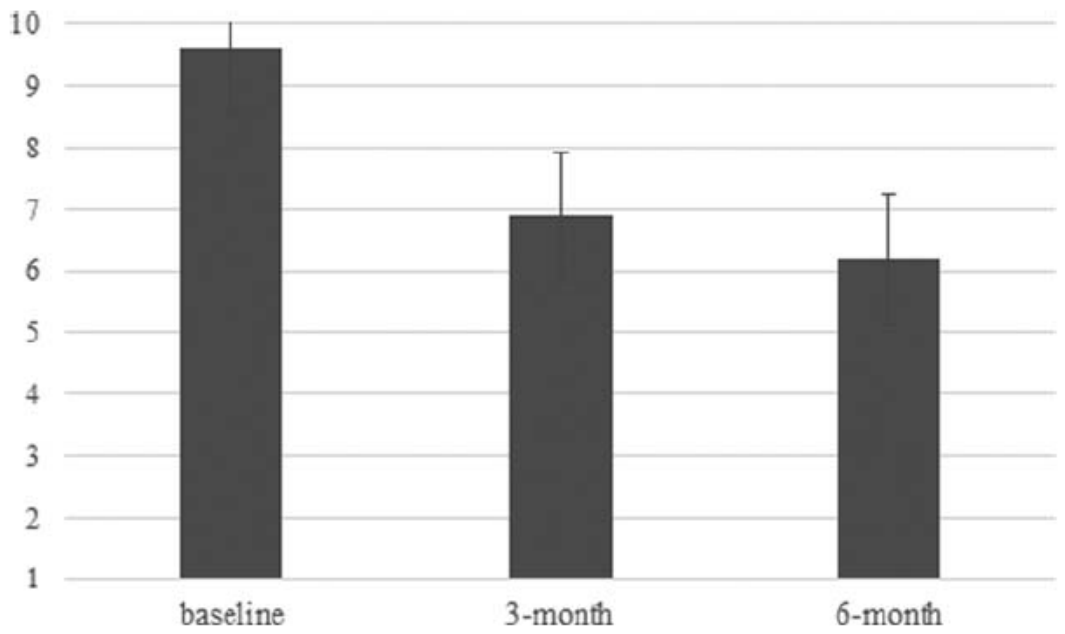


Figure 2 In the liraglutide group, EAT (measured in mm) decreased from 9.6 ± 2 to 6.8 ± 1.5 and 6.2 ± 1.5 mm ($P < 0.001$) after 3 and 6 months, respectively.

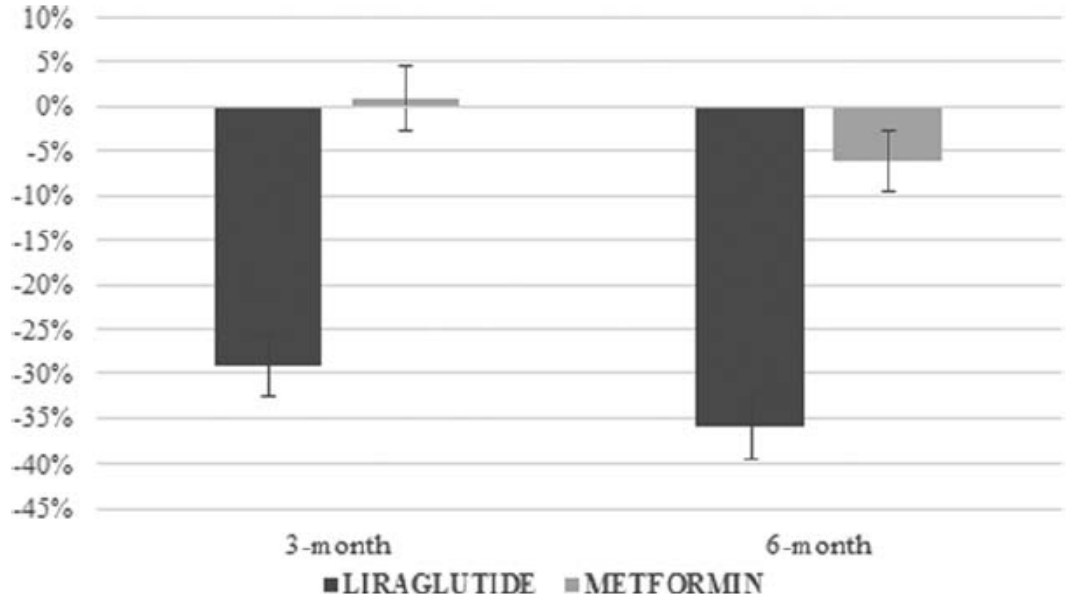


Figure 3 In the liraglutide group, EAT decreased by 29% and 36% at 3 and 6 months, respectively, whereas there was no significant EAT reduction in the metformin group (+1% and −4% at 3 and 6 months, respectively.

Ultrasound-measured EAT thickness was measured at baseline and at 3- and 6-month follow-ups

Iacobellis et al 2017

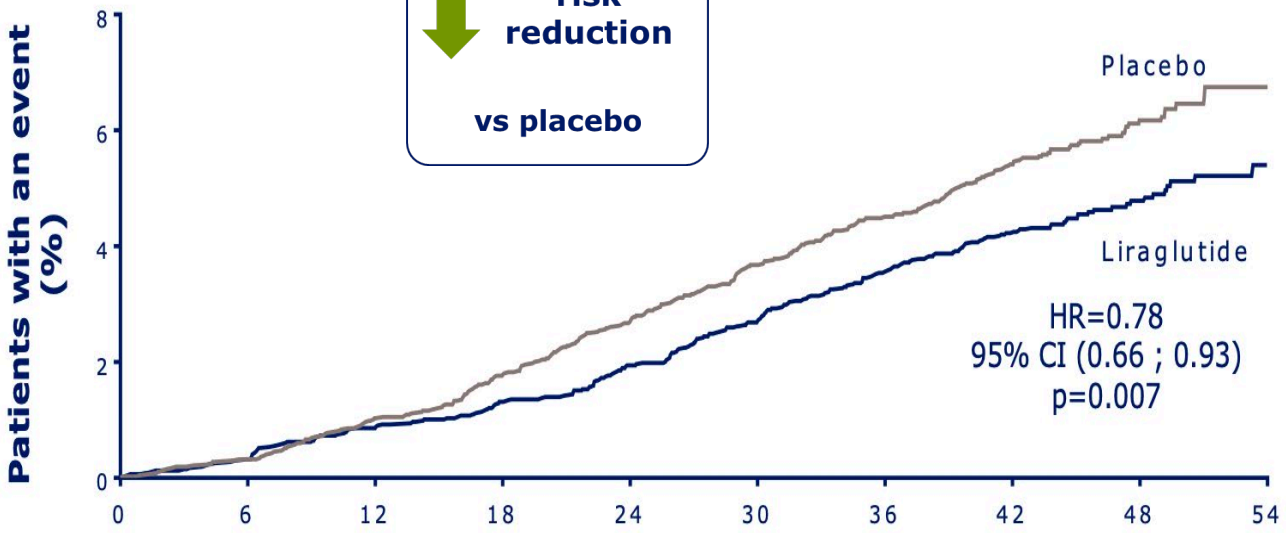
STUDIO LEADER

CV death

Primary outcome:
CV death, non-fatal MI or non-fatal stroke

22%
risk reduction

vs placebo



Patients at risk

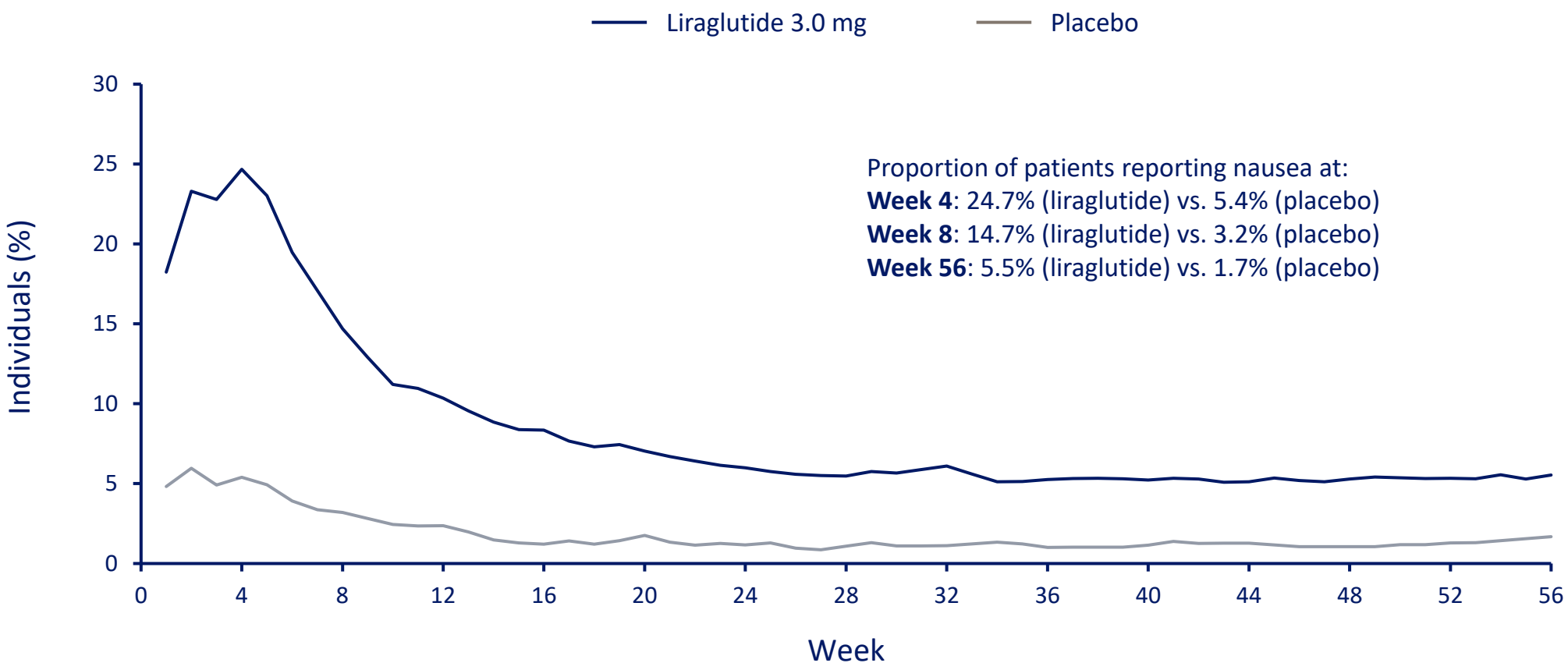
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

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

N Engl J Med 2016. DOI: 10.1056/NEJMoa1603827

Proportion of individuals with nausea

SCALE Obesity and Prediabetes: 0-56 weeks

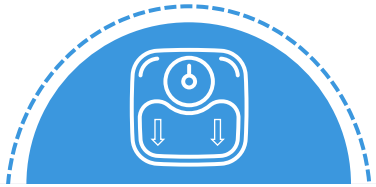


Proportion of patients reporting nausea at:
Week 4: 24.7% (liraglutide) vs. 5.4% (placebo)
Week 8: 14.7% (liraglutide) vs. 3.2% (placebo)
Week 56: 5.5% (liraglutide) vs. 1.7% (placebo)

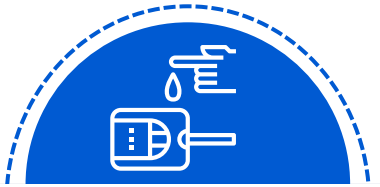
Safety analysis set
Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Conclusion

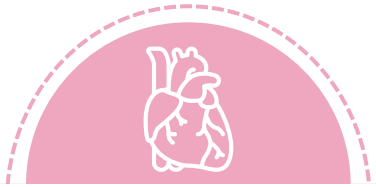
Liraglutide 3.0 mg once daily, in combination with a reduced-calorie diet as well as physical activity, significantly lowered visceral and ectopic fat compared to placebo



Greater percentages of patients were able to achieve 5%, 10% and 15% weight loss with liraglutide compared with placebo. Common weight regain problem after RYGB surgery can be addressed by liraglutide 3.0 mg



There was also significant reduction in the glycemia levels and inflammation in patients treated with liraglutide compared to placebo group.

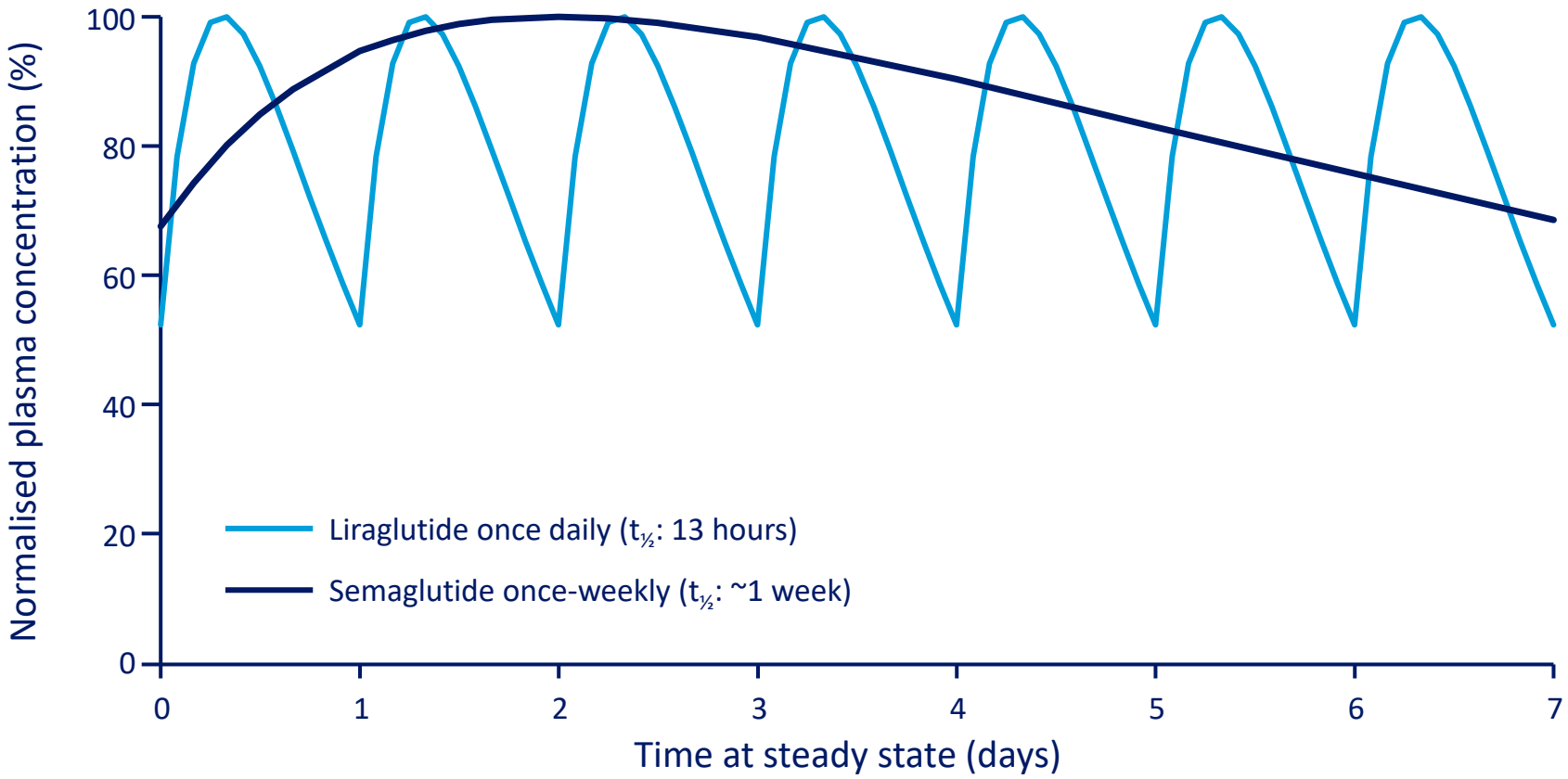


Findings suggest that visceral and ectopic fat reduction could be a mechanism underpinning the CVD risk benefit seen with liraglutide in patients with type 2 diabetes

CVD, Cardiovascular;
Neeland et al. The Lancet Diabetes & Endocrinology 2021; 9(9): 595-605

Il prossimo futuro….

Semaglutide provides more constant plasma levels compared with liraglutide

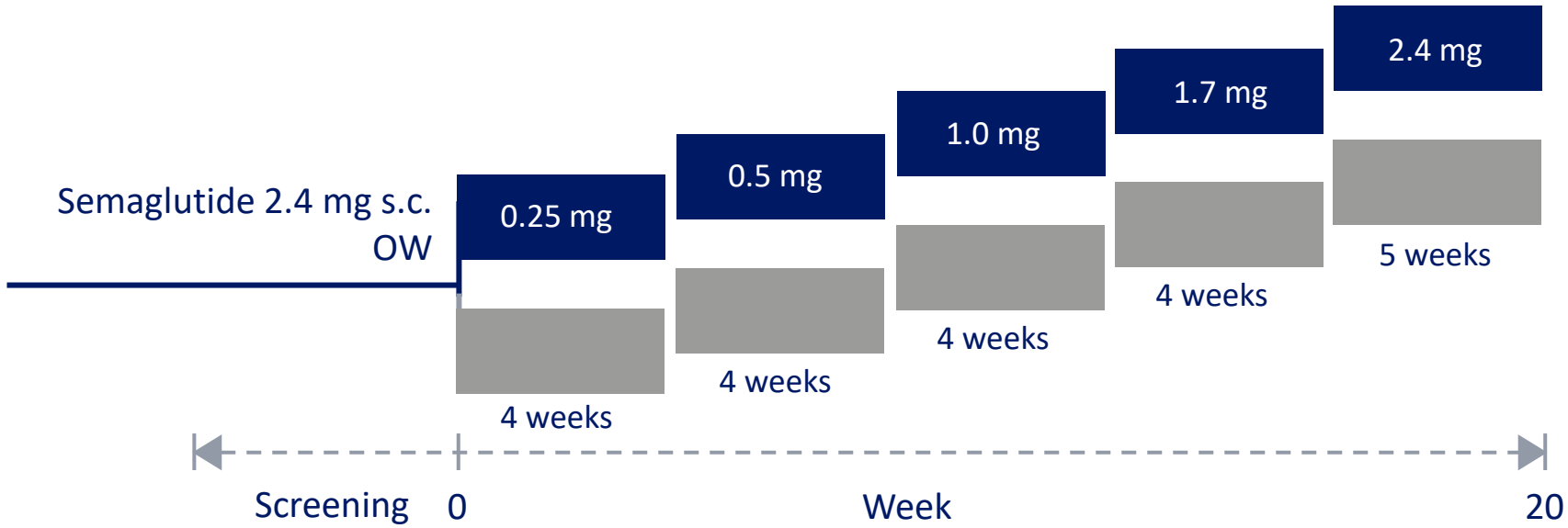


Profiles were based on simulated modelling. Liraglutide is the only GLP-1RA that is approved by the US FDA and EMA for use in overweight/obese participants without T2D. It is dosed once daily.
EMA, European Medicines Agency; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; t½, half life.
Elbrønd et al. Diabetes Care 2002;25:1398–404; Marbury et al. Clin Pharmacokinet 2017;56:1381–90; Novo Nordisk. Data on file.

SOMMINISTRAZIONE DI SEMAGLUTIDE

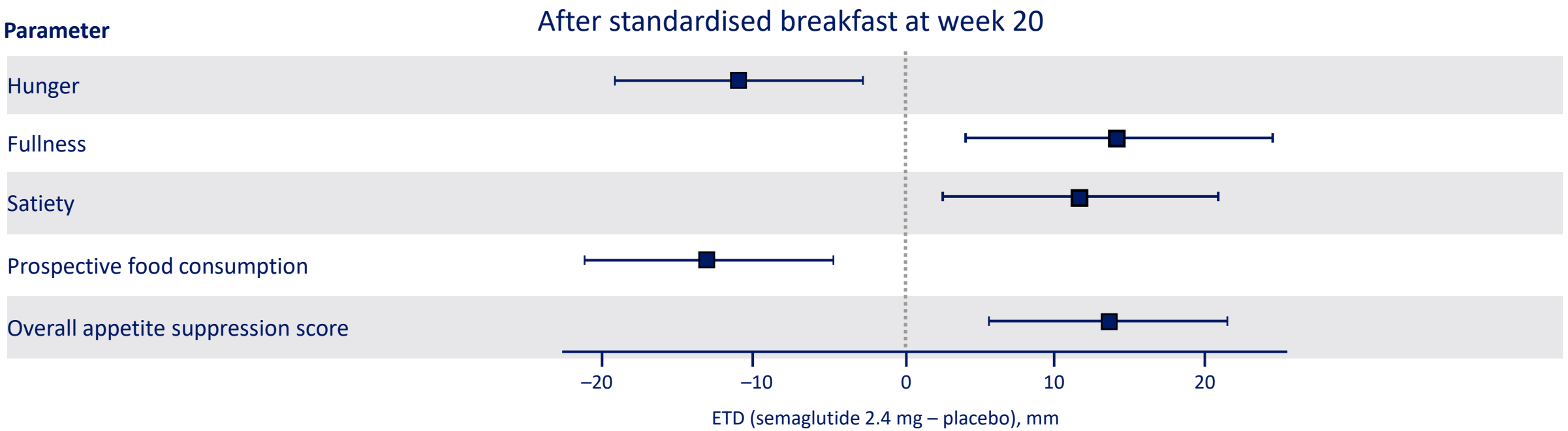
Once a Week S.C. con incrementi ogni 4 settimane: dalla dose di 0,25mg/OW alla dose ottimale di mantenimento di 2,4mg/OW

NB: la dose massimale settimanale di Semaglutide per la terapia del Diabete è di 1mg/die !



Semaglutide impacts all dimensions of appetite

Participants with obesity

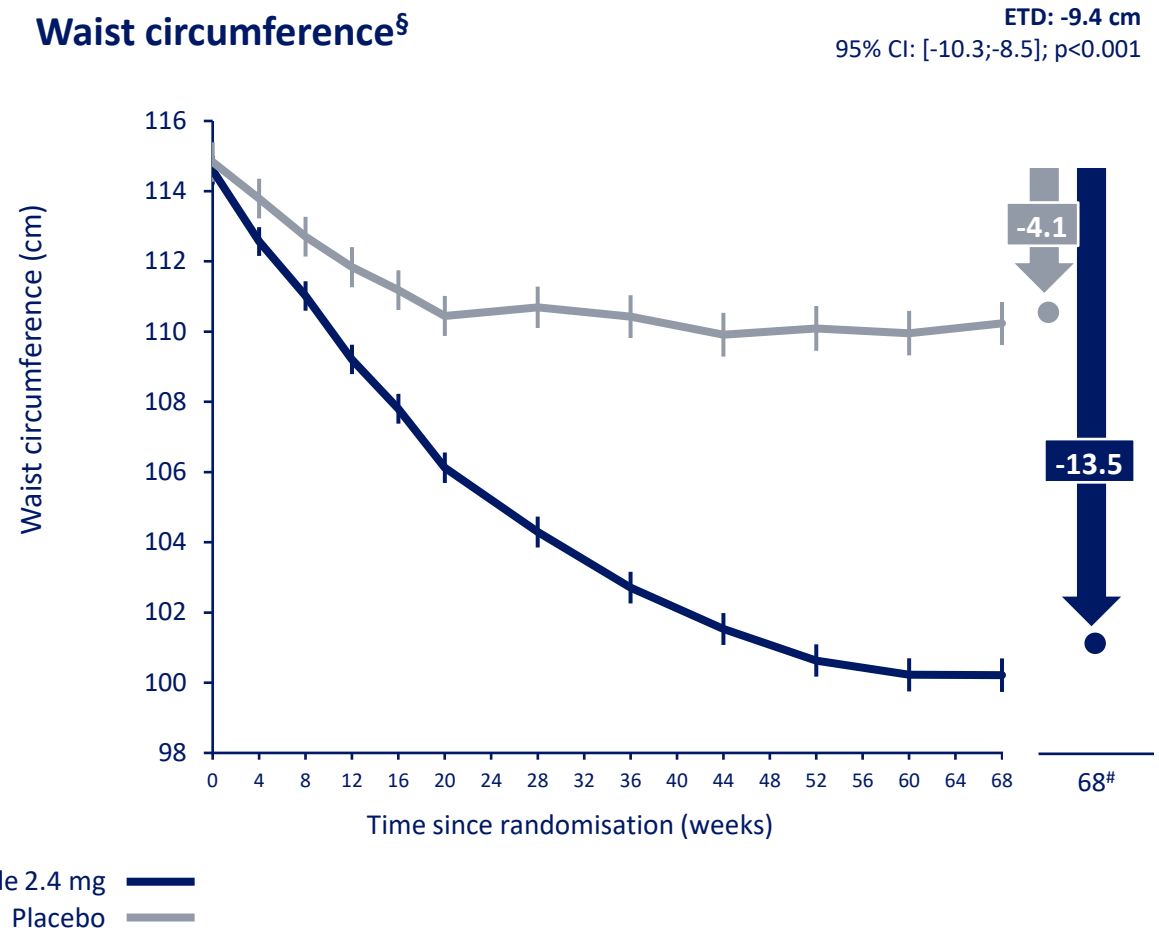


After a standardised breakfast, hunger and prospective food consumption were reduced, and fullness and satiety increased, with semaglutide 2.4 mg vs placebo (all p≤0.01)

ETD, estimated treatment difference.
Friedrichsen et al. Diabetes Obes Metab 2021;23:754–62.

Change in waist circumference

STEP 1

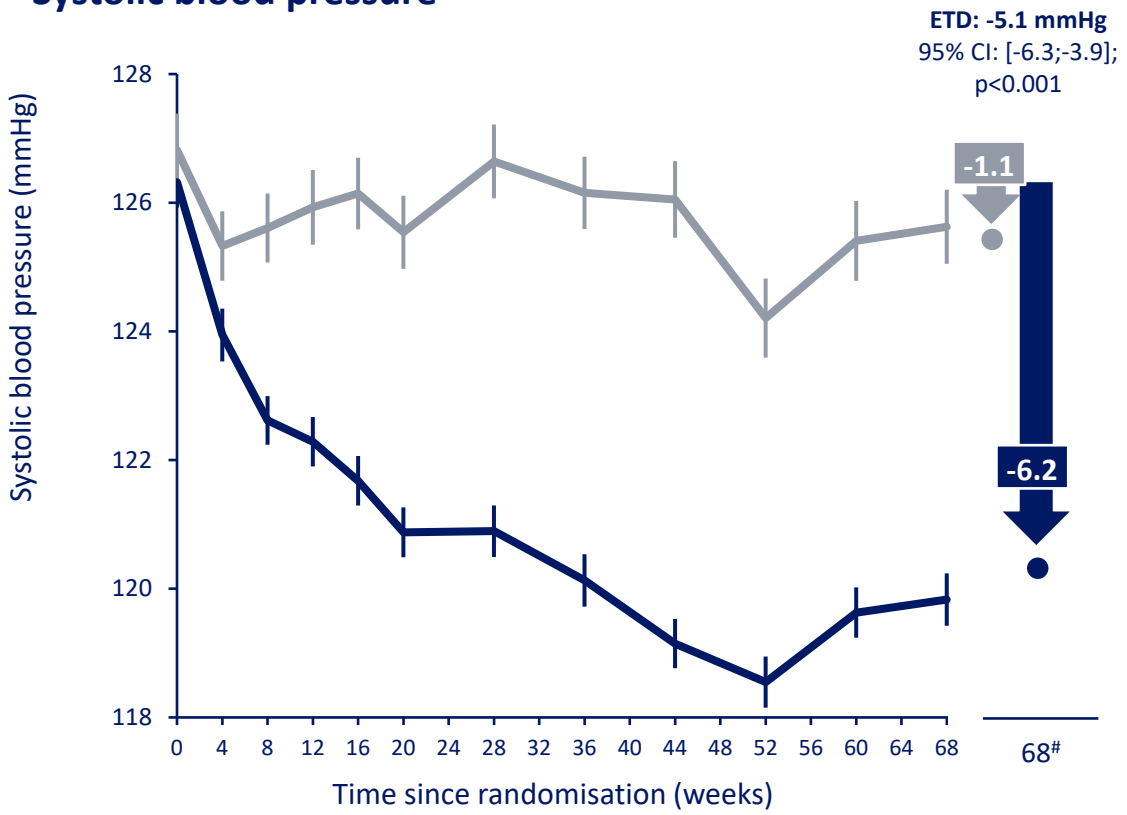


§ Means are based on observed data from the in-trial period and the ETD is for the treatment policy estimand. Error bars are +/- standard error of the mean.
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference.
Wilding et al. N Engl J Med 2021;384:989-1002.

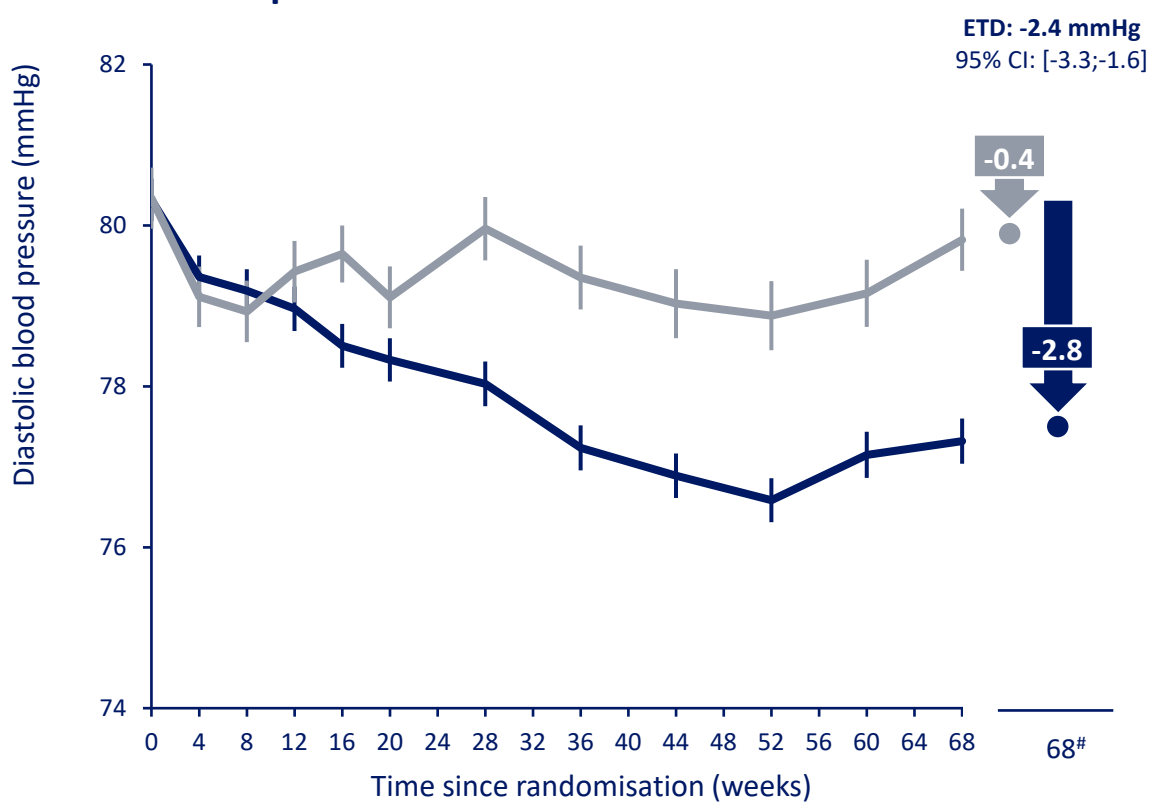
Change in blood pressure

STEP 1

Systolic blood pressure§



Diastolic blood pressure§



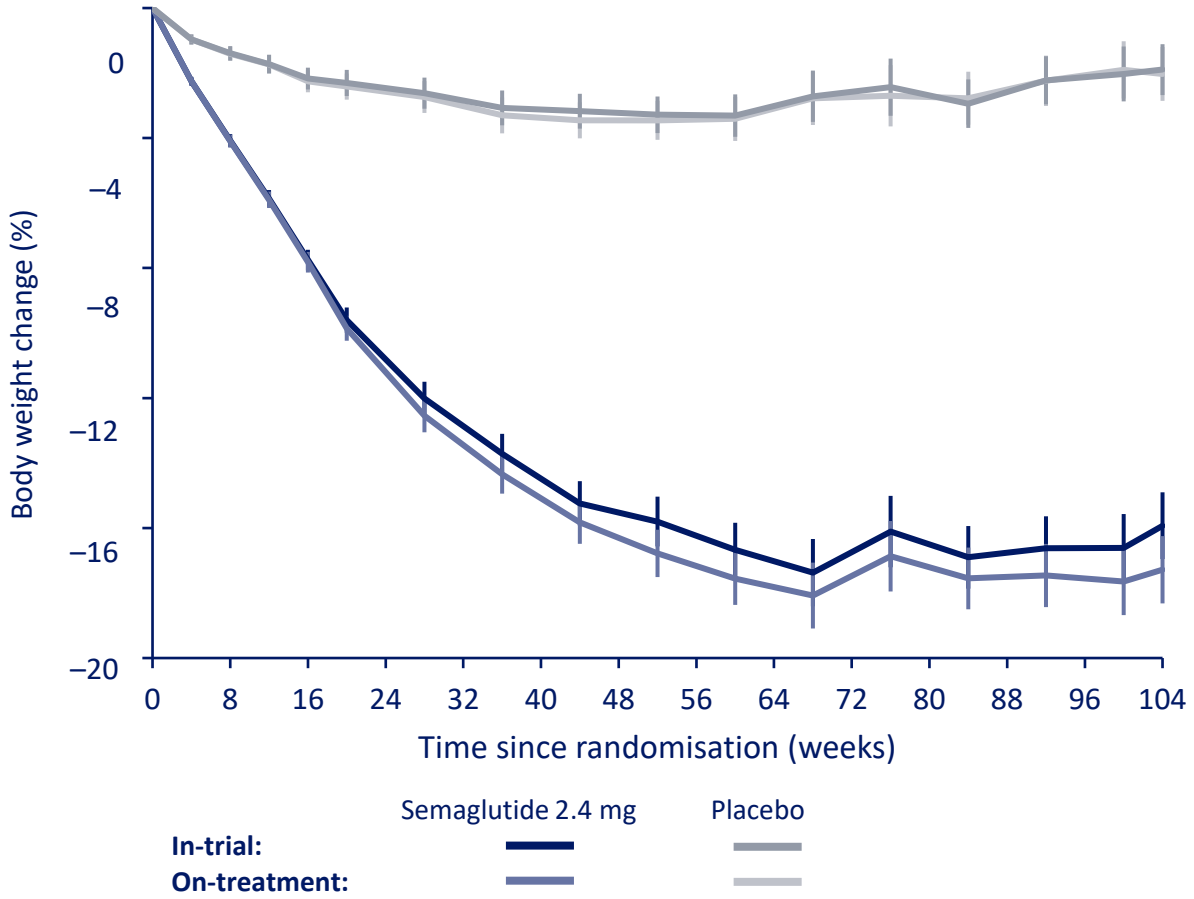
Semaglutide 2.4 mg
Placebo

§ Means are based on observed data from the in-trial period and the ETD is for the treatment policy estimand. # Estimated values at week 68.
Error bars are +/- standard error of the mean. CI, confidence interval; ETD, estimated treatment difference.
Wilding et al. N Engl J Med 2021;384:989-1002.

Body weight change

STEP 5

Observed mean change over time
(Mean at baseline: 106.0 kg)



Treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention); Trial product estimand assesses treatment effect if trial product was taken as intended.
CI, confidence interval; ETD, estimated treatment difference.
Garvey et al. Nature Medicine 2022; 28(10): 2083-2091

nature medicine

Article

https://doi.org/10.1038/s41591-023-02526-x

Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial

nature medicine

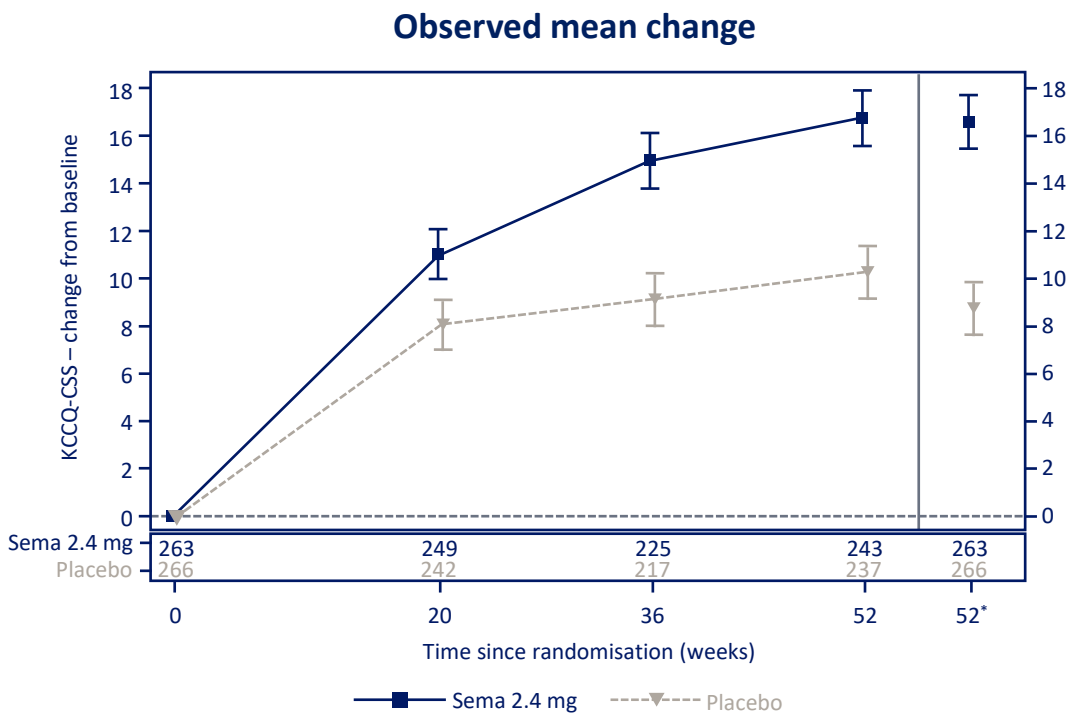
Article

https://doi.org/10.1038/s41591-023-02526-x

Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial

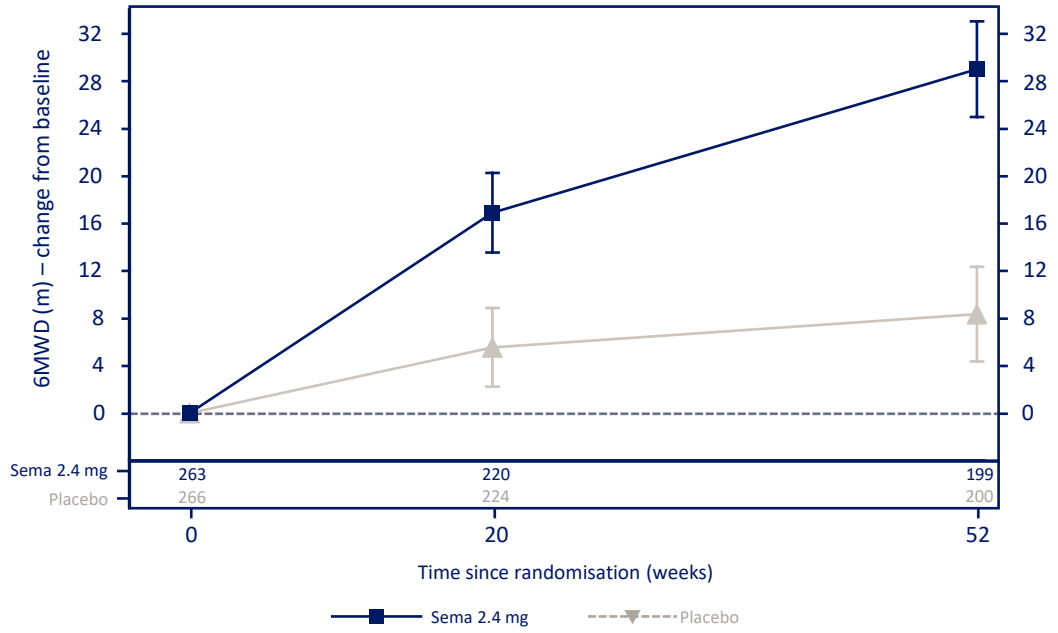
Significant improvement in mean **KCCQ-CSS** with semaglutide 2.4 mg vs placebo at week 52

Primary endpoint



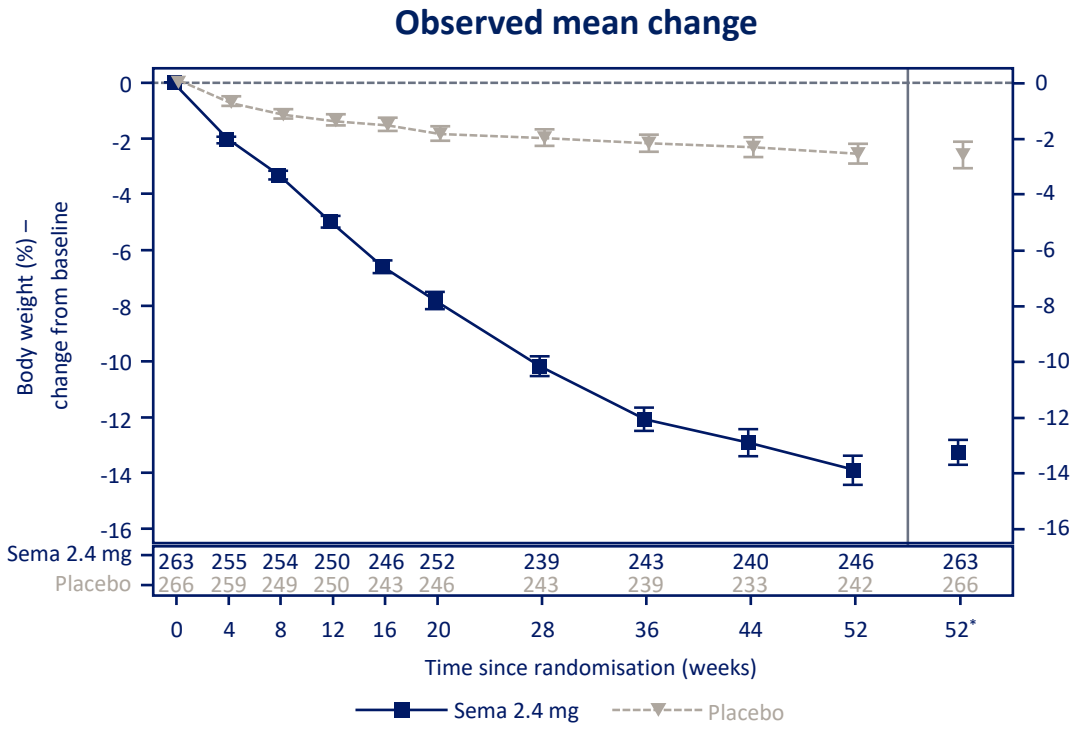
Significant increase in mean **6MWD** with semaglutide 2.4 mg vs placebo

Confirmatory secondary endpoint



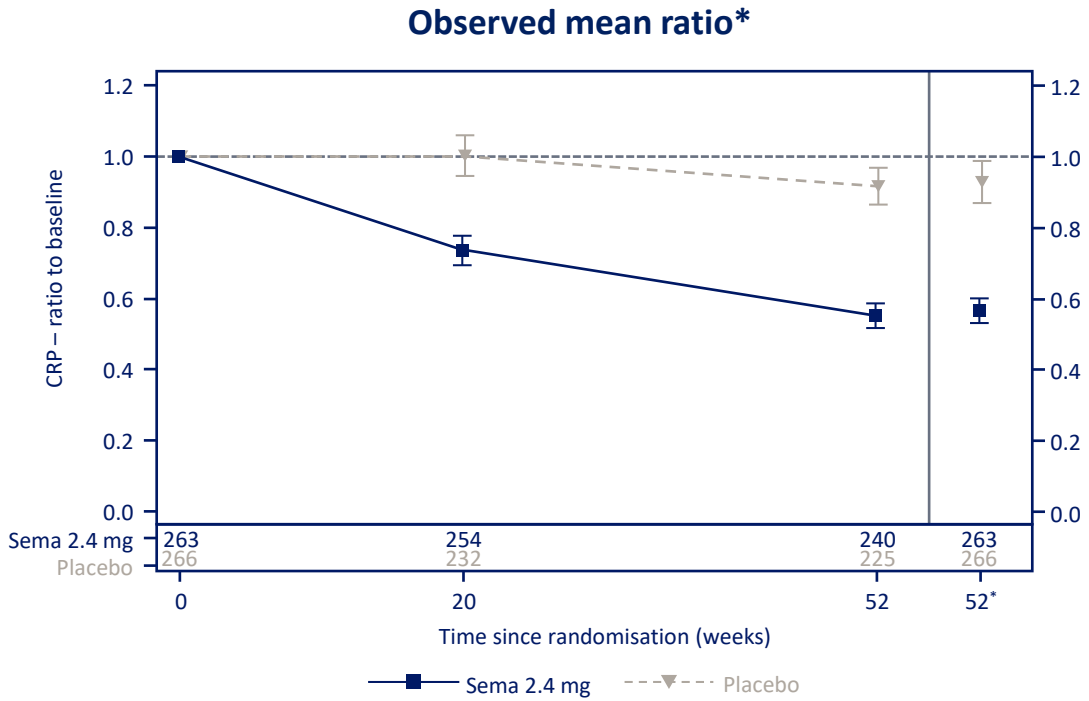
Significant decrease in mean **body weight** with semaglutide 2.4 mg vs placebo

Primary endpoint



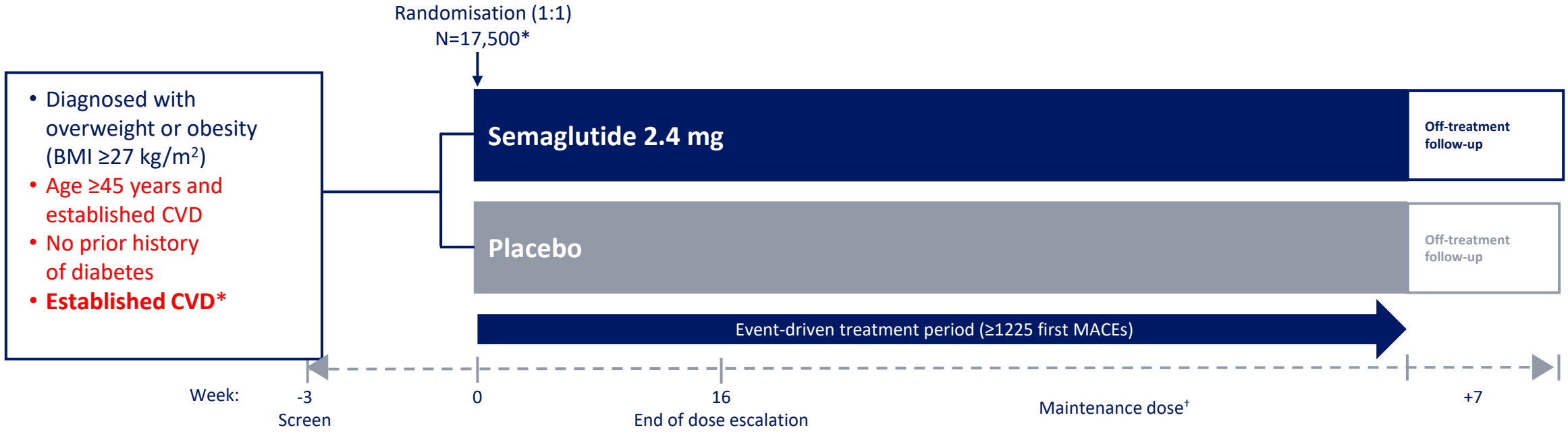
Significant decrease in CRP levels with semaglutide 2.4 mg vs placebo

Confirmatory secondary endpoint



SELECT: Semaglutide CVOT

Trial design (NN9536-4388)



Trial information

- Double-blind, parallel group, placebo-controlled superiority trial
- FPFV 24 Oct 2018

Trial objective

To demonstrate that semaglutide 2.4 mg OW lowers the incidence risk of MACE vs placebo both added to SoC in participants with established CVD and overweight or obesity

Key endpoints

Primary: Time from randomisation to first occurrence of MACE (non-fatal MI, non-fatal stroke, CV death)

Secondary: Time from randomisation to CV death or all-cause death

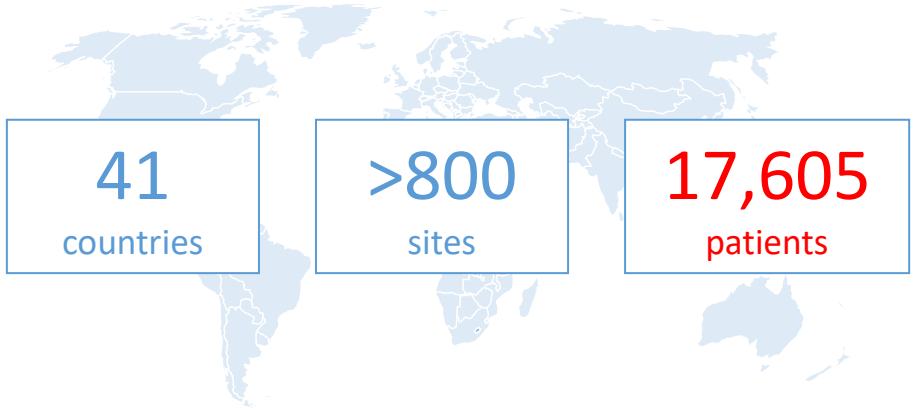
**Anticipated. †Dose escalation is Week 0 to 4 and maintenance dose is event-driven to end of treatment period.*
CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; FPFV, first patient first visit; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; OW, once-weekly; PAD, peripheral artery disease; SoC, standard of care.

SELECT: trial overview

Primary objective[1]

To demonstrate that s.c. semaglutide 2.4 mg OW lowers the incidence of MACE versus placebo, both added to SoC, in people with established CVD and overweight or obesity

Key trial numbers[1]



Trial design[1,2]

- **Overweight or obesity**
- **Established CVD***
- **No prior history of diabetes**

Semaglutide 2.4 mg OW

Placebo

Event-driven (≥1,225 first MACE)
~5 years

SELECT-LIFE[3]

10-year post-trial observational follow up to assess potential long-term effects of anti-obesity medication

**Established CVD: MI ≥60 days ago, stroke ≥60 days ago, or symptomatic PAD, NYHA class IV excluded.*
CV, cardiovascular; CVD, CV disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; OW, once weekly; PAD, peripheral artery disease; s.c. subcutaneous; SoC, standard of care.

1. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 2. Ryan DH et al. Am Heart J 2020;229:61–9; 3. ClinicalTrials.gov. SELECT-LIFE. Available at: https://clinicaltrials.gov/ct2/show/NCT04972721. Accessed January 2023.

Semaglutide 2.4 mg reduces the risk of major adverse cardiovascular events by 20%

SELECT: Adults with overweight or obesity and established CVD

AMERICAN COLLEGE of CARDIOLOGY

Obesity, Cardiovascular Disease, and the Promising Role of Semaglutide: Insights from the SELECT Trial

Hamza Irfan MBBS

- **The study's primary endpoint was the composite outcome of the first occurrence of MACE* defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.** [1]
- **All three components making up the primary endpoint contributed to the 20% MACE reduction exhibited in the semaglutide 2.4 mg treatment group. Over a period of up to five years, 1,270 first MACE events occurred.**[1]

- The results also aligned with the safety and patient tolerance of the weekly 2.4 mg semaglutide injections, confirming previous findings regarding the same treatment.[2]

**The primary endpoint of the study was defined as the composite outcome of the first occurrence of MACE, defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.*

1,American College of Cardiology, SELECT: Semaglutide Reduces Risk of MACE in Adults With Overweight or Obesity, Accessed October 2023, https://www.acc.org/Latest-in-Cardiology/Articles/2023/08/10/14/29/SELECT-Semaglutide-Reduces-Risk-of-MACE-in-Adults-With-Overweight-or-Obesity. 2. Irfan H. Obesity, Cardiovascular Disease, and the Promising Role of Semaglutide: Insights from the SELECT Trial. Curr Probl Cardiol. 2023 Aug 26;49(1 Pt A):102060. doi: 10.1016/j.cpcardiol.2023.102060. Epub ahead of print. PMID: 37640171.

MACE, major adverse cardiovascular events; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity.

Conclusioni

- Liraglutide 3,0 mg e Semaglutide 2,4 mg hanno portato a riduzioni significative del peso corporeo rispetto al placebo, prolungate anche dopo 2/3 anni di trattamento.
- hanno migliorato i fattori di rischio cardiometabolico, tra cui circonferenza vita, SBP, DBP, CRP, HbA1c e trigliceridi rispetto al placebo
- La sicurezza e la tollerabilità erano coerenti con la classe GLP-1RA in generale
- I risultati degli studi supportano un profilo rischio-beneficio favorevole per la gestione del peso a lungo termine nelle persone con sovrappeso o obesità

CRP, C-reactive protein; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.
Garvey et al. Nature Medicine 2022; 28(10): 2083-2091; Wharton et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.