EASO
European Association for the Study of Obesity

EASO Summer School: Masterclass in the Prevention and Management of Obesity

Les Pensières at Fondation Mérieux. Annecy, France: 11 - 15 July 2022

Different Treatment Options for Different Levels of Care

EASOCOM
EASO Collaborating Centre for Obesity Management

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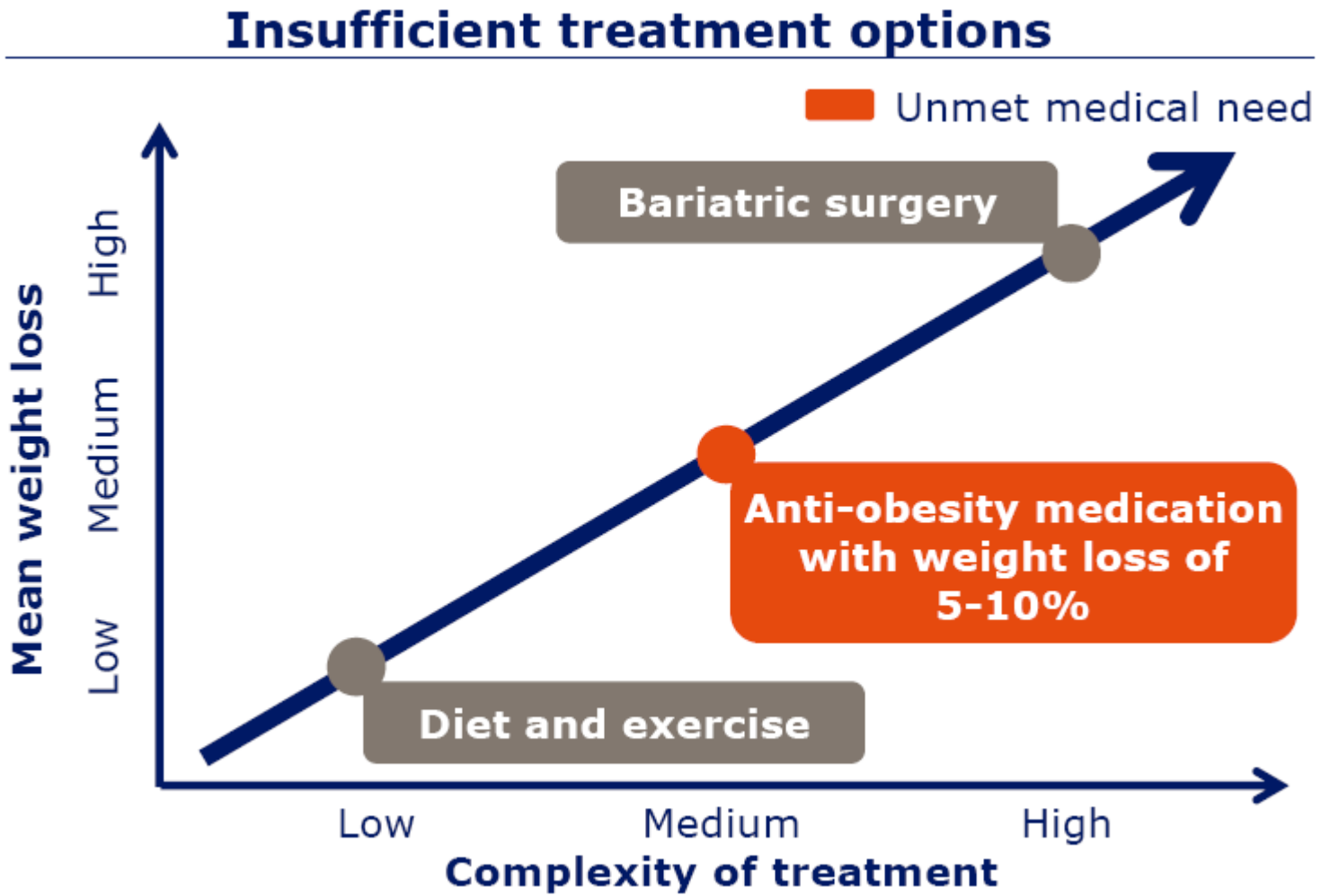
Società Italiana dell'Obesità
RETE CENTRI ACCREDITATI PER LA CURA DELL'OBESITA'

Department of Systems Medicine
Internal Medicine Unit
and Obesity Center
University Hospital Policlinico Tor Vergata

Proportionality in obesity management



Delivery of tiered obesity services (UK)

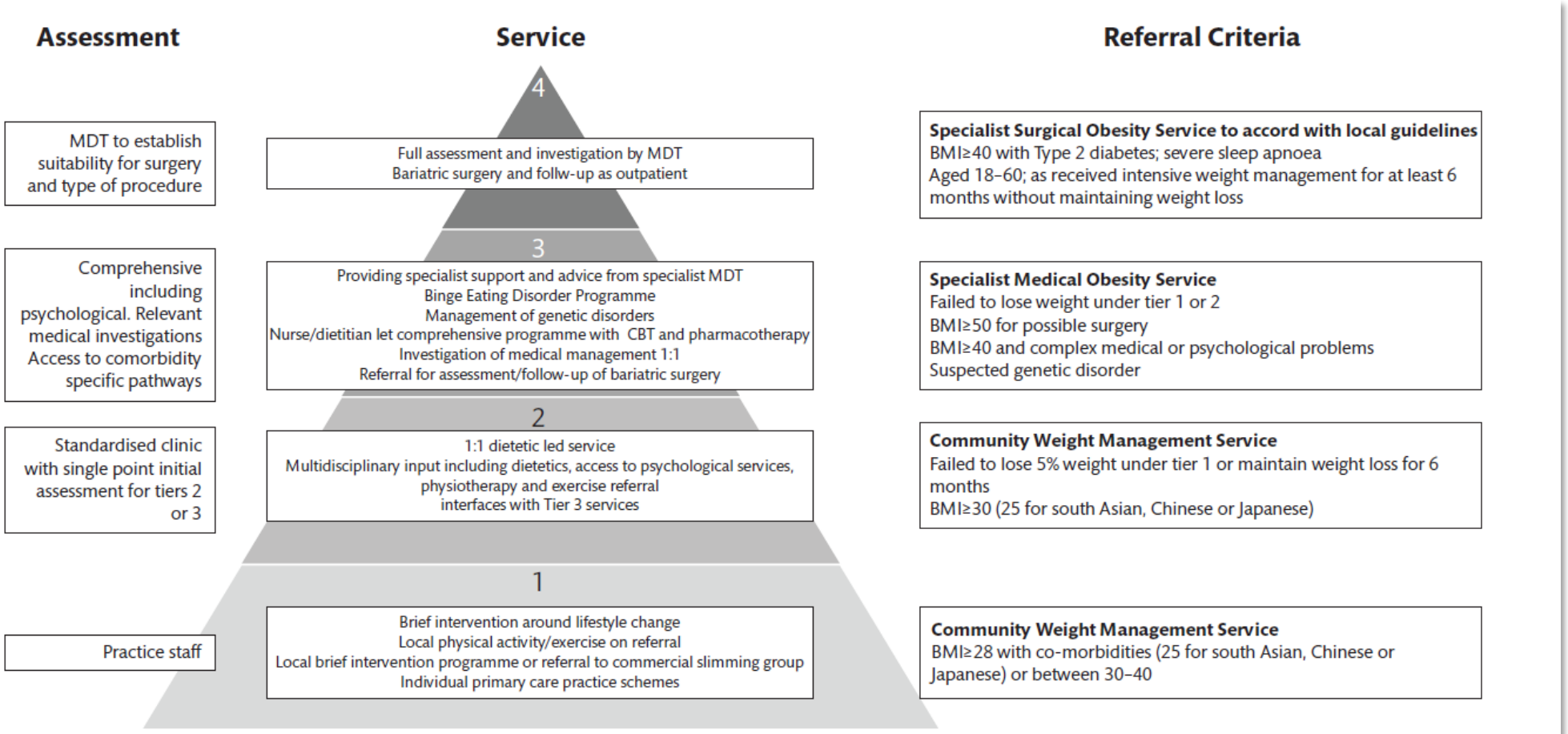


Figure 14.1.8.3 An example from the east of England of delivery of tiered obesity services. MDT, multidisciplinary team.

Adapted with permission from Brett B, Ahmed A. Addressing the Obesity Challenge in the East of England—A report to the East of England Clinical Senate Assembly Public Health England, 2017. Contains public sector information licensed under the Open Government Licence v3.0. [24]

Treatment Algorithm of Patients with Overweight and Obesity

EOSS	BMI < 30	BMI 30-35	BMI 35-40	BMI >40	Age (years)
STAGE 0					> 60
					< 60
STAGE 1				S	> 60
					< 60
STAGE 2				S	> 60
					< 60
STAGE 3			S	S	> 60
					< 60
STAGE 4					> 60
		S	S	S	< 60

lifestyle intervention

pharmacological therapy
(In patients with T2DM, is indicated the use of antidiabetic medications that have additional actions to promote weight loss, such as GLP-1 analogs).

bariatric surgery

rehabilitation (physical, neurological, cardiopulmonary, psychiatric)

S surgery to be considered in selected cases with favorable risk/benefit profile

Santini F, Busetto L, Cresci B and Sbraccia P, Eat Weight Disord, 2016

NICE National Institute for Health and Care Excellence

Level of intervention to discuss with the patient

BMI classification	Waist circumference: low	Waist circumference: high	Waist circumference: very high	Comorbidities present
Overweight	1	2	2	3
Obesity I	2	2	2	3
Obesity II	3	3	3	4
Obesity III	4	4	4	4

Levels of intervention

1	General advice on healthy weight and lifestyle
2	Diet and physical activity
3	Diet and physical activity; consider drugs
4	Diet and physical activity; consider drugs; consider surgery

2014

Obesity in adults: a clinical practice guideline

- Canadian Guideline -

Step 3: Discussion of treatment options

Adults living with obesity should receive individualized care plans that address their root causes of obesity and that provide support for behavioural change (e.g., nutrition, physical activity) and adjunctive therapies, which may include psychological, pharmacologic and surgical interventions.

CMAJ, 2020

A NEW FRAMEWORK FOR THE DIAGNOSIS, STAGING AND MANAGEMENT OF OBESITY DISEASE IN ADULTS

- EASO work in progress -

- Choose the appropriate initial level of intervention (behavioral modifications alone, psychological therapy, obesity medications, bariatric procedures) based more on the individual therapeutic goal, the clinical severity of obesity and the previous obesity treatments, rather than on anthropometric parameters only.

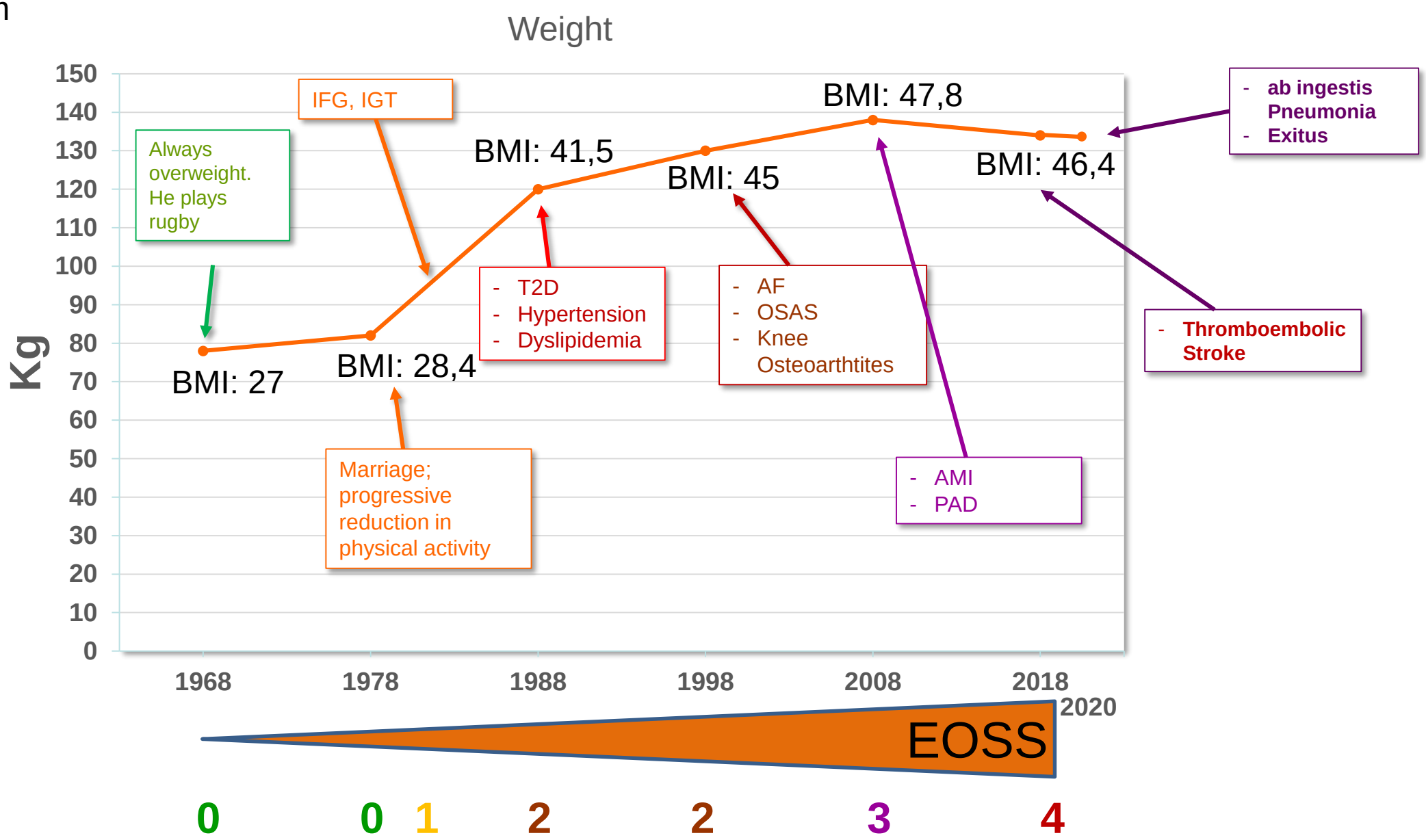
Conditions needed for the proportionality approach to be efficacious

- The different stages of the process of interest should be, at least in the majority of cases, independent each other (*i.e., overweight does not necessarily develop into obesity, and so on*).
- In the cases in which there is a progression toward the subsequent stages, the force of progression should be proportionate to the degree of the stage (milder in overweight, very strong in obesity class III).

Does the proportionality approach always hold true in Obesity?

- If obesity is a progressive disease, we should expect that initial milder level of intervention may be insufficient.
- Within chronic diseases there is a documented tendency toward therapeutic inertia.

♂ A. F.
Born 1948;
Height: 170 cm



Does the proportionality approach always hold true?

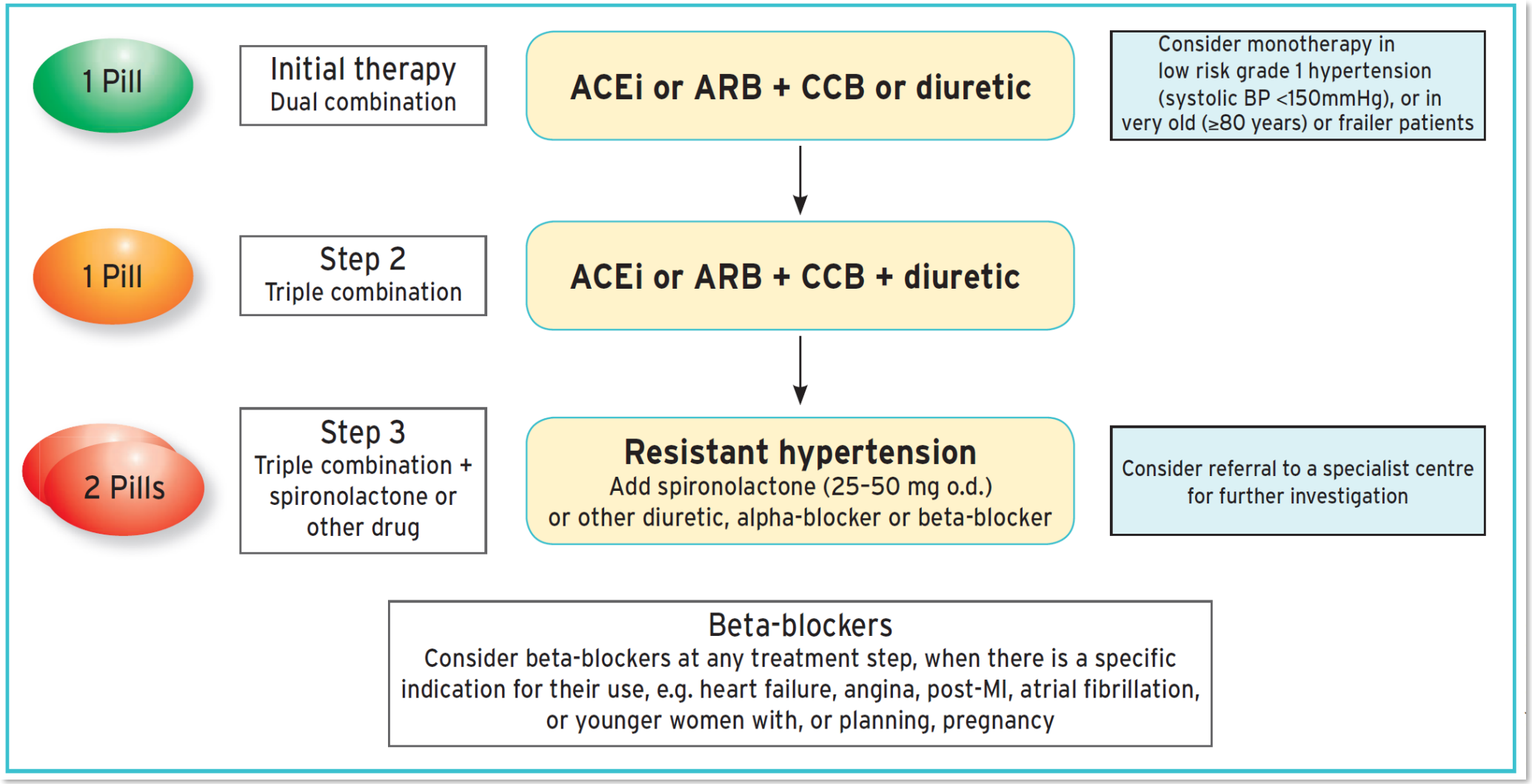
- If obesity is a progressive disease, we should expect that initial milder level of intervention may be insufficient.
- Within chronic diseases there is a documented tendency toward therapeutic inertia.
- If milder initial level of intervention does not fulfill the patients' expectations they will tend to withdraw them, even if it induces an improvement in health status.

A NEW FRAMEWORK FOR THE DIAGNOSIS, STAGING AND MANAGEMENT OF OBESITY DISEASE IN ADULTS

- EASO work in progress -

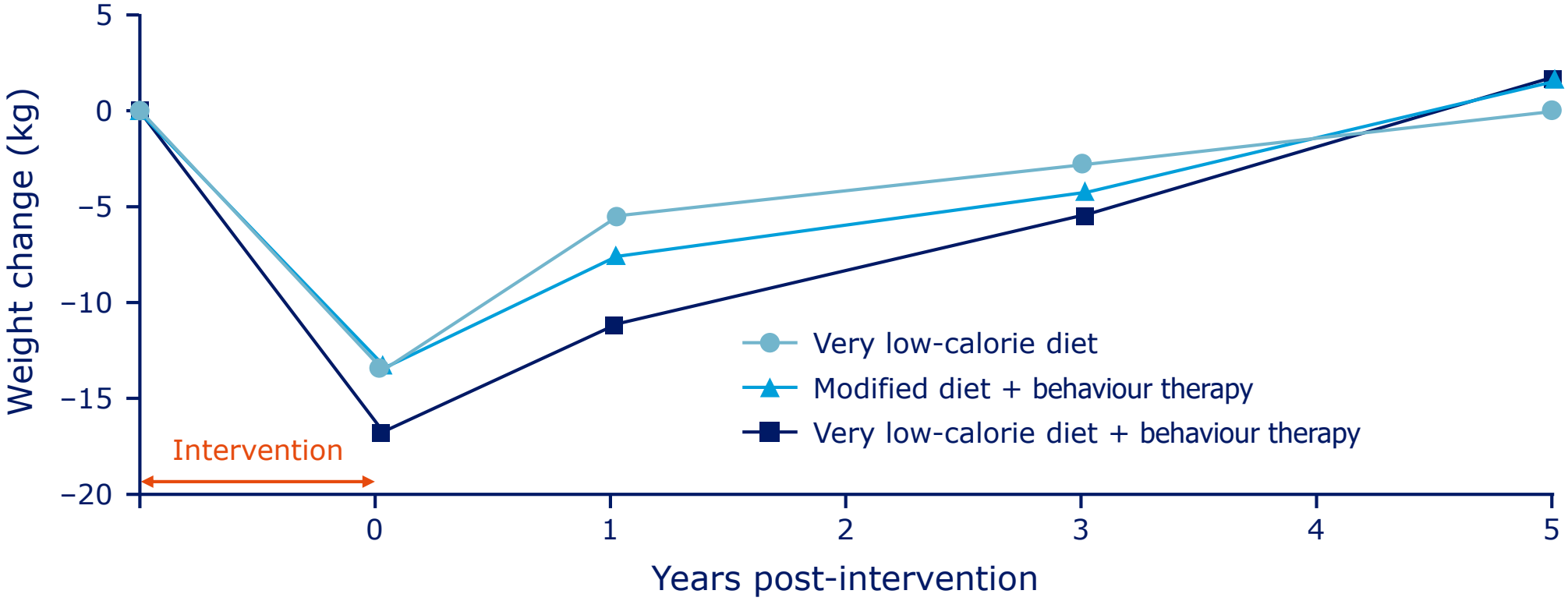
- Consider promptly intensification of therapy or add additional therapies if the initial level of intervention is not sufficient to achieve the individual therapeutic goal.

2018 ESC/ESH Guidelines for the Management of Arterial Hypertension



Williams et al, Eu Heart J 2018

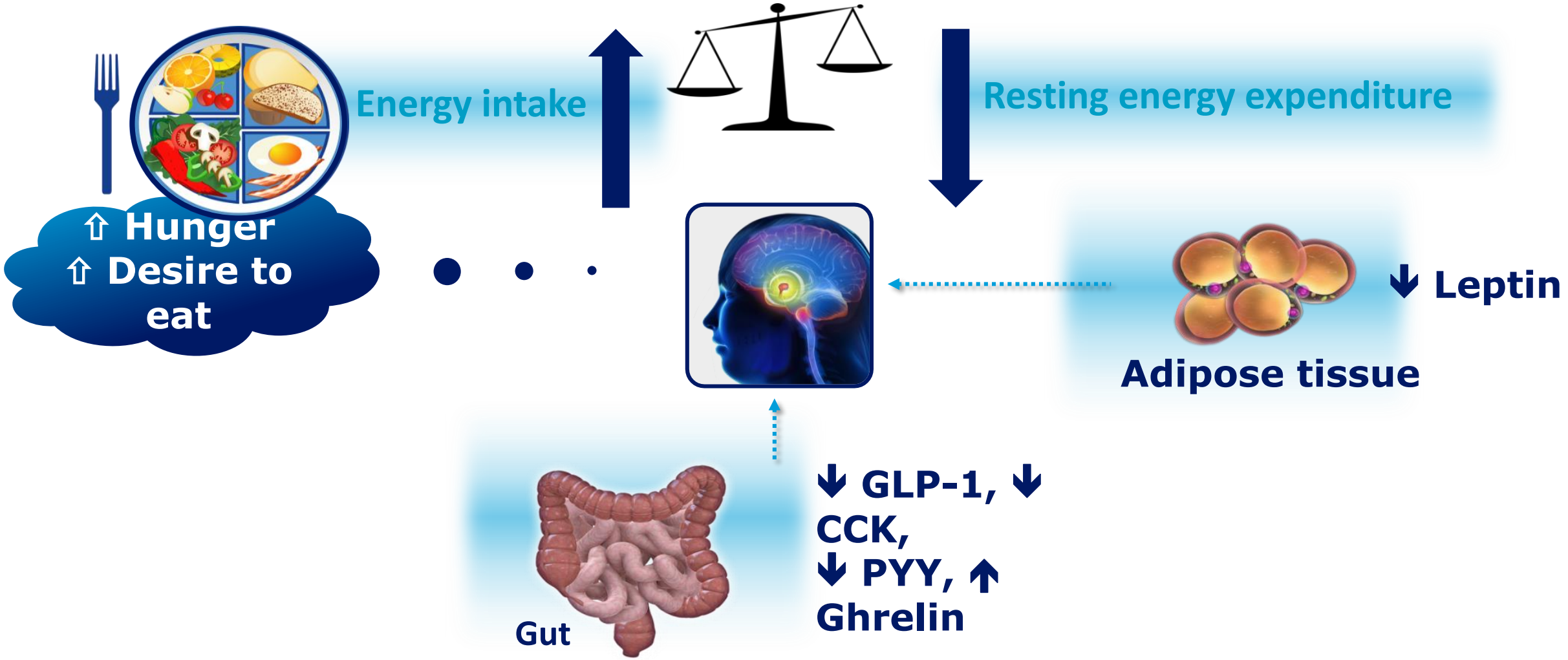
Weight management interventions are often followed by weight rebound



Data are from diet and behavioural interventions

Wadden *et al*. *Ann Intern Med* 1993;119:688–93

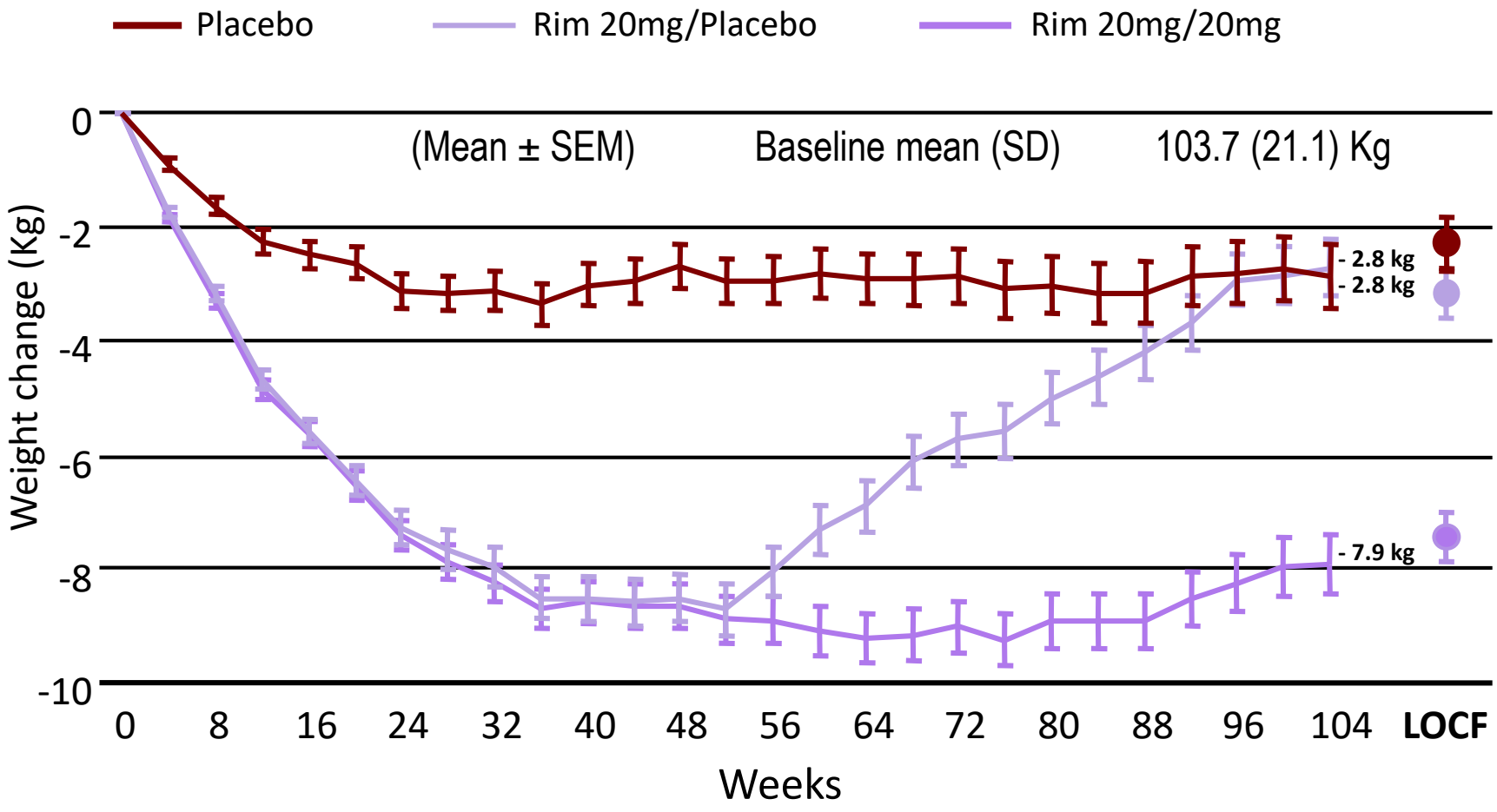
Physiological responses to weight loss favour weight regain



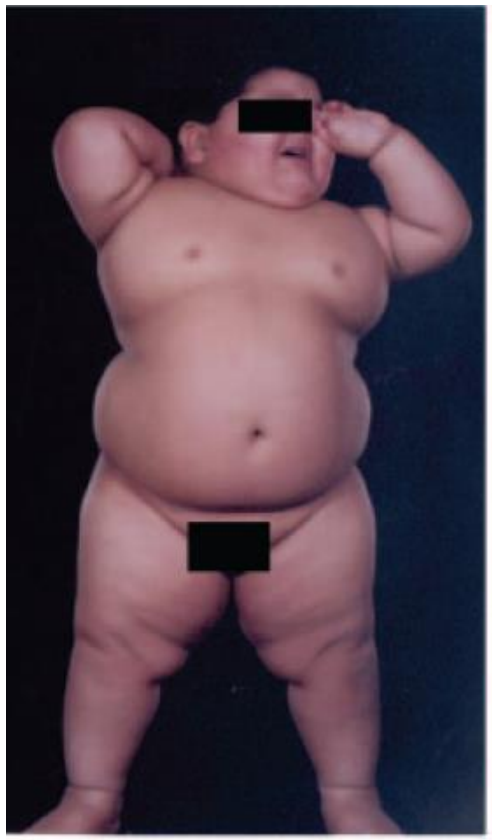
CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY

Schwartz A et al. *Obes Rev* 2010;11:531–547; Sumithran P et al. *N Engl J Med* 2011;365:1597–1604

2 yr re-randomisation trial shows need for continued drug use



X. Pi-Sunyer, Circulation 2005:111(13);1727



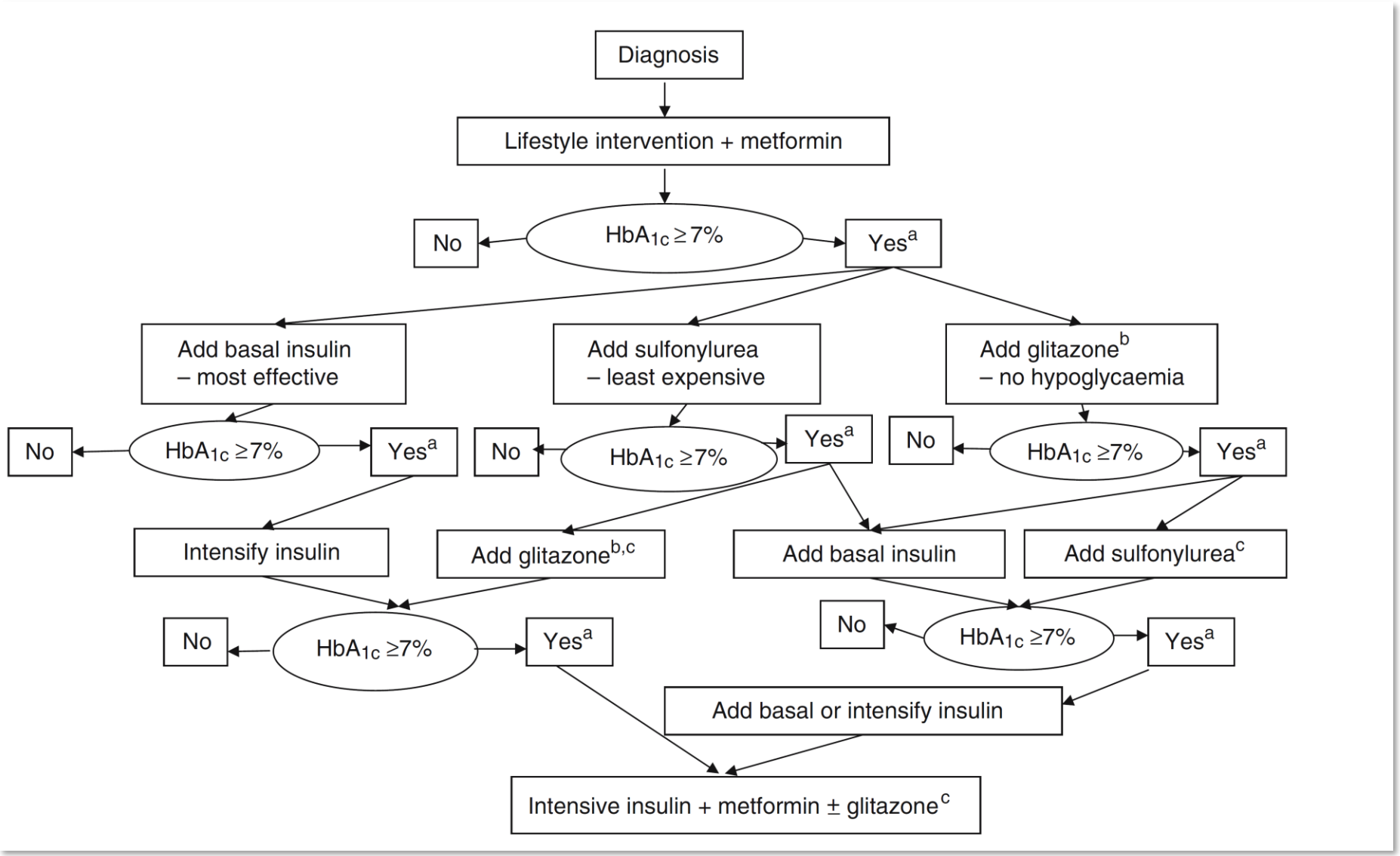
weight = 40kg, age 3yrs

Treatment guidelines are molded by pharmacologic advancements

- Treatment guidelines are molded by the development of new drugs with new MoA.

Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

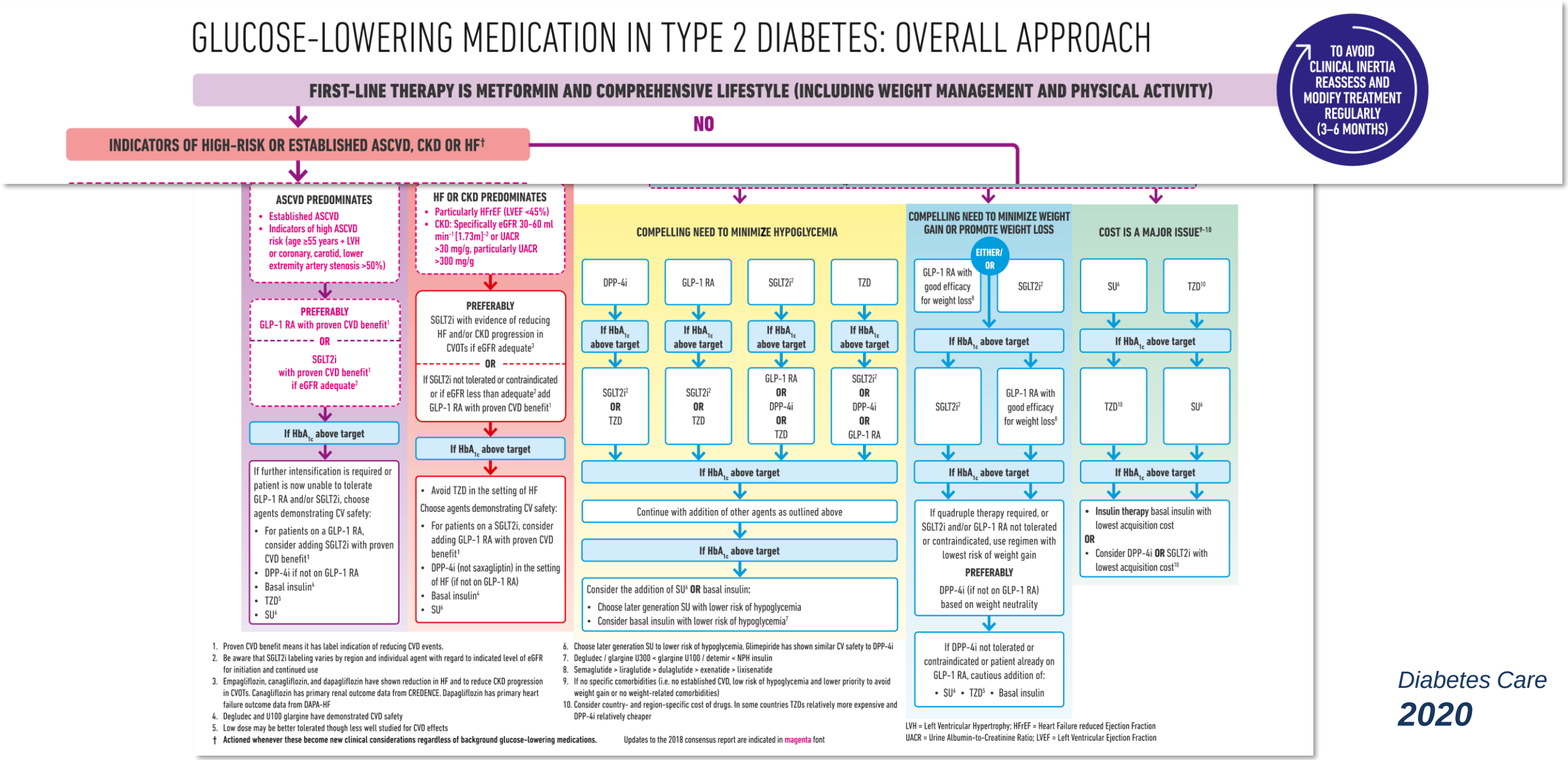
EASD - ADA



Diabetes Care
2008

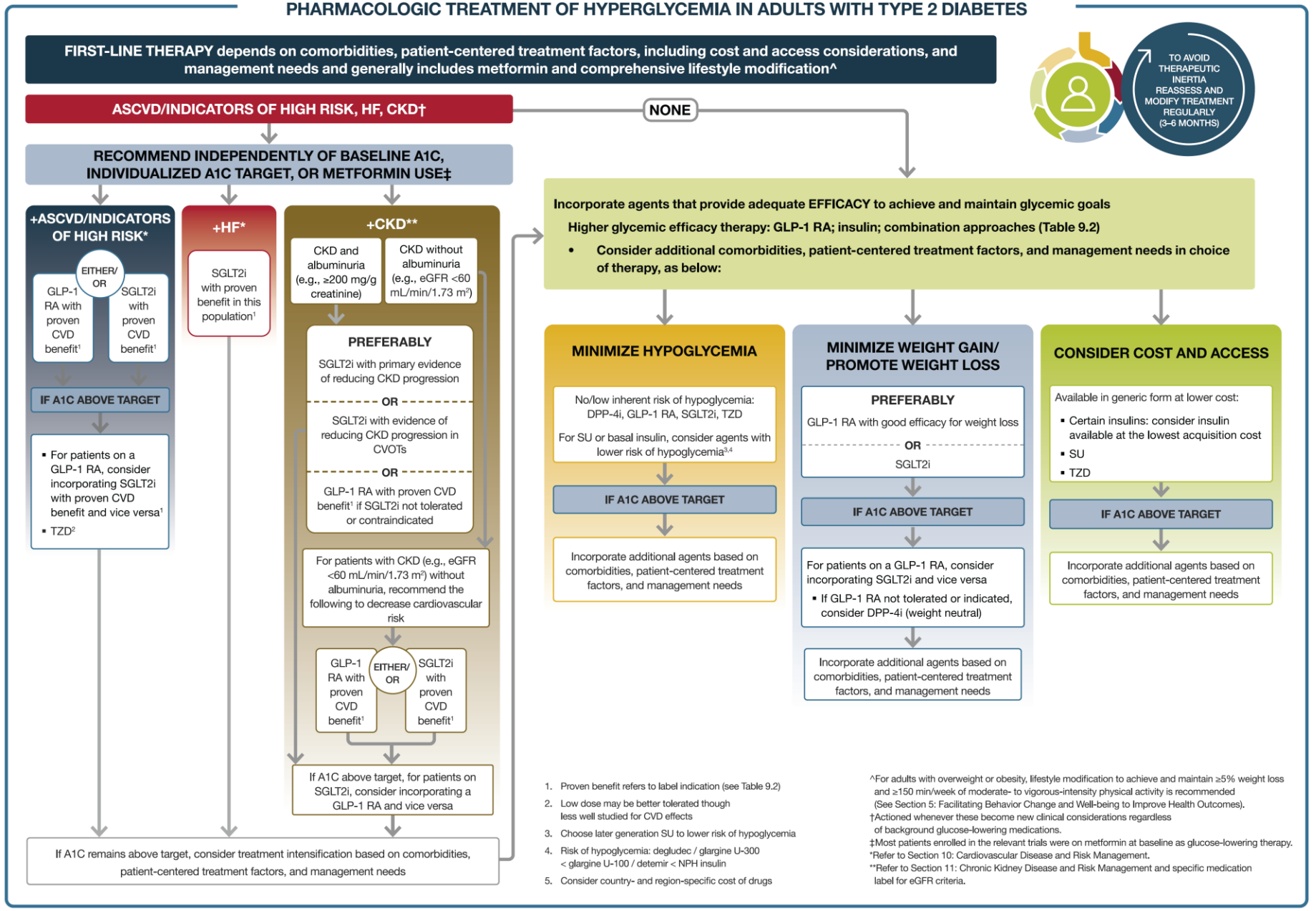
2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018.

EASD - ADA



Diabetes Care
2020

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2022

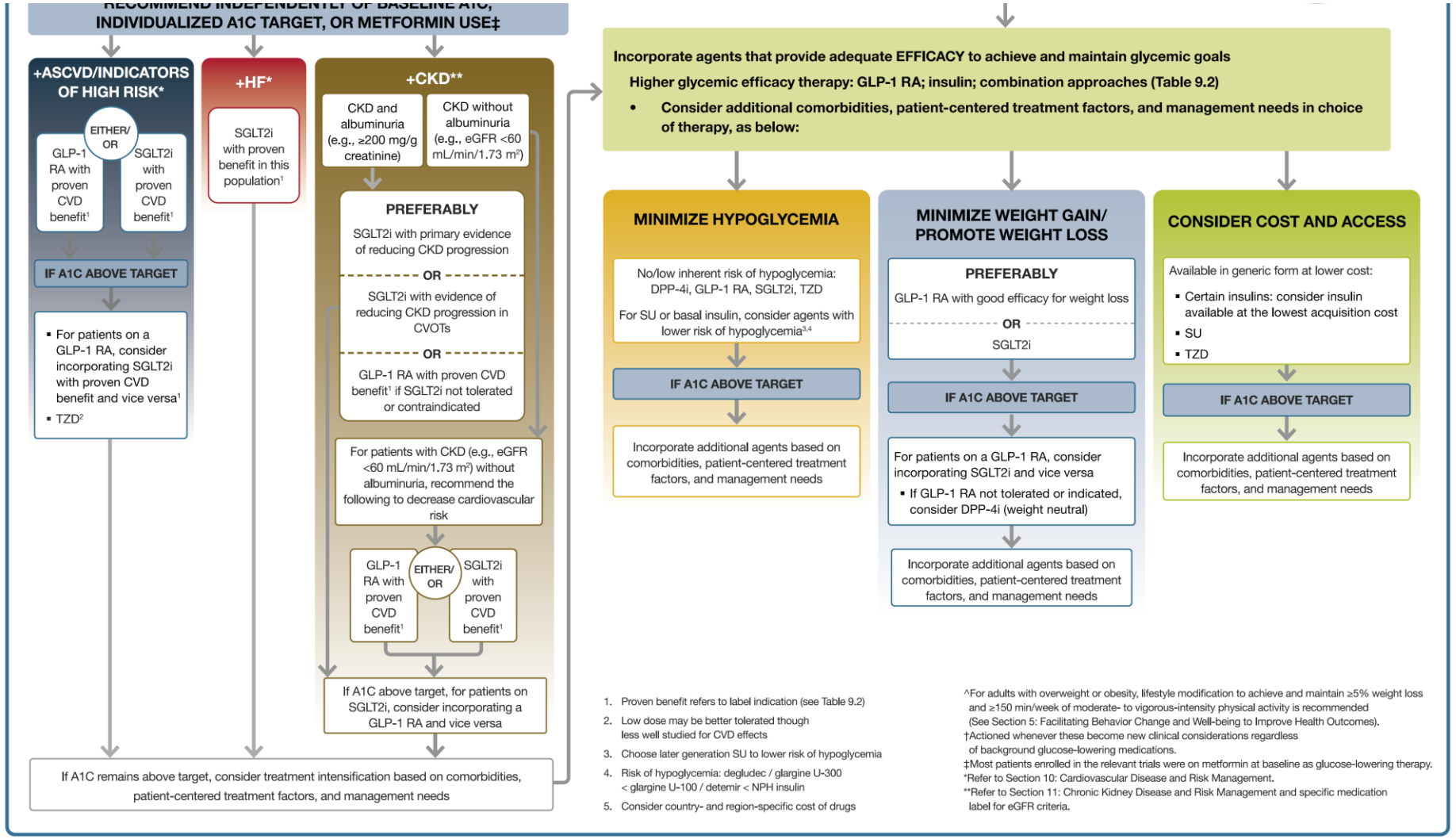


Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2022

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABET

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^



Diabetes Care 2022;45(Suppl. 1):S125–S143

ELEMENTS TO TAKE INTO ACCOUNT WHEN CHOSING AN AOM

- Efficacy
- % Non-responders

- Efficacy in improving complications:
  diabetes, hypetension, NASH, dislypidemia, CV, OSAS, eating disorders, depression etc.

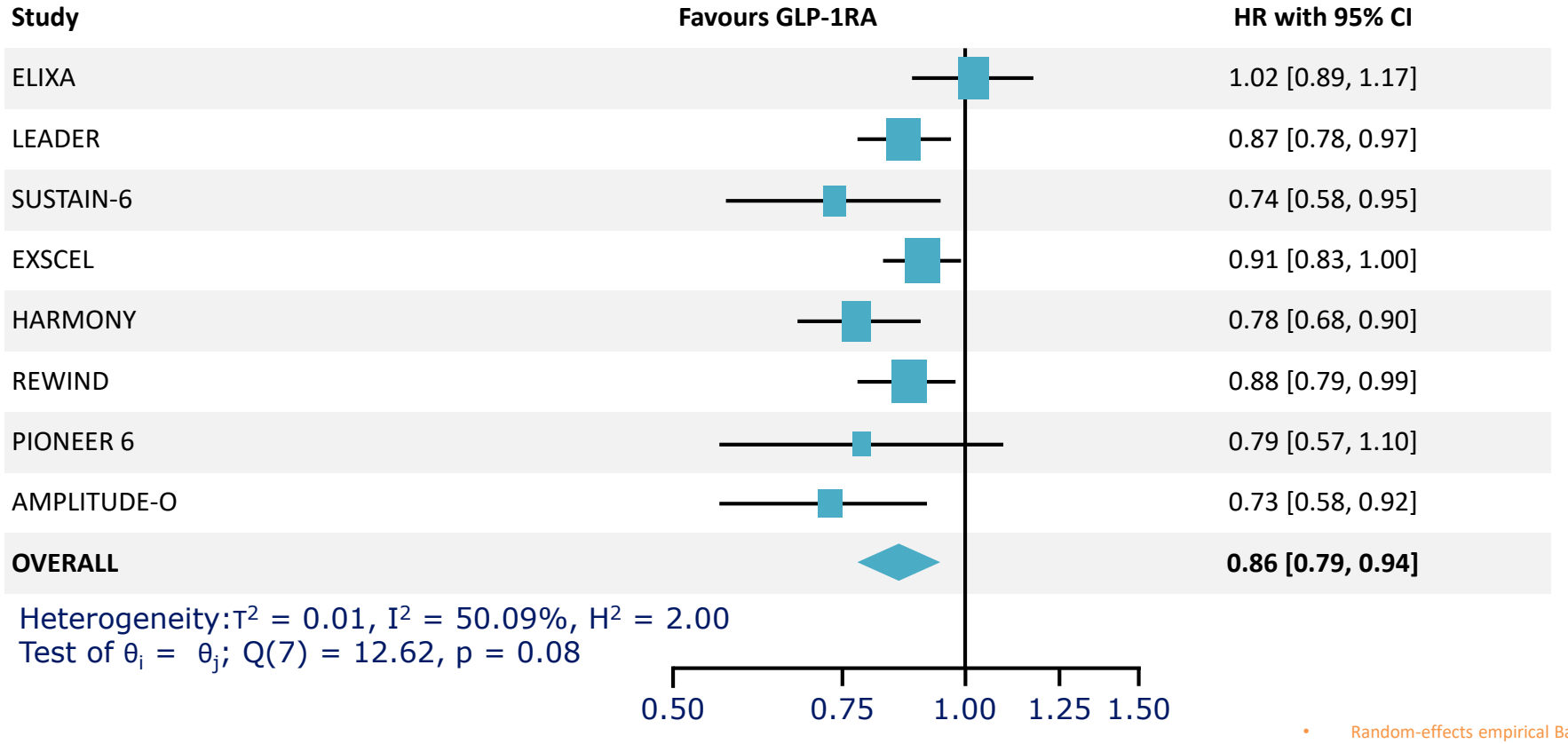
- Safety:
  CV, neuropychitric, etc

- Efficacy related to phenotype:
  waist, body composition, age, *sedentariness, etc.*

GLP-1RA cardiovascular outcomes trials revealed beneficial cardiovascular effects in people with T2D

What about people with obesity at increased cardiovascular risk?

Major cardiovascular adverse events



- Random-effects empirical Bayes model Knapp-Hartung standard errors
- Giugliano D, et al. Cardiovasc Diabetol. 2021;20:189

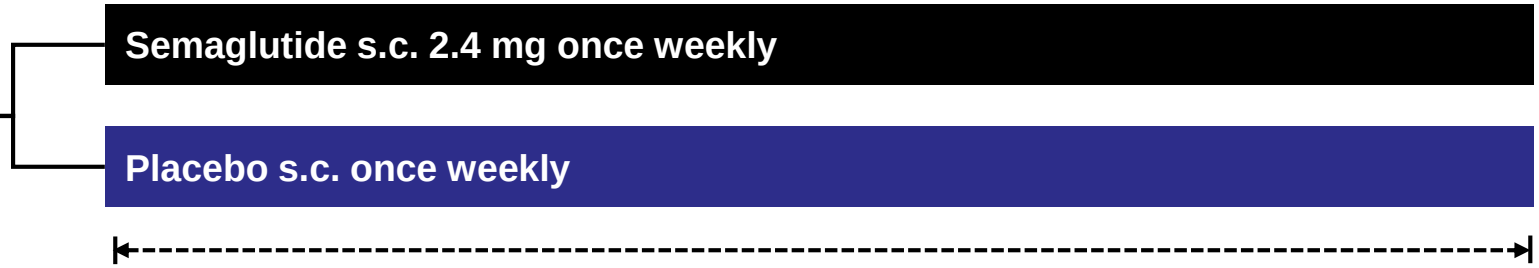
SELECT: a CVOT in patients with overweight or obesity and CVD

Trial design

Primary objective

To demonstrate that s.c. semaglutide 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in patients with established CV disease and overweight or obesity

N=17,500 patients
BMI: ≥27 kg/m^2
Established CVD
Screening
HbA_{1c} <6.5%



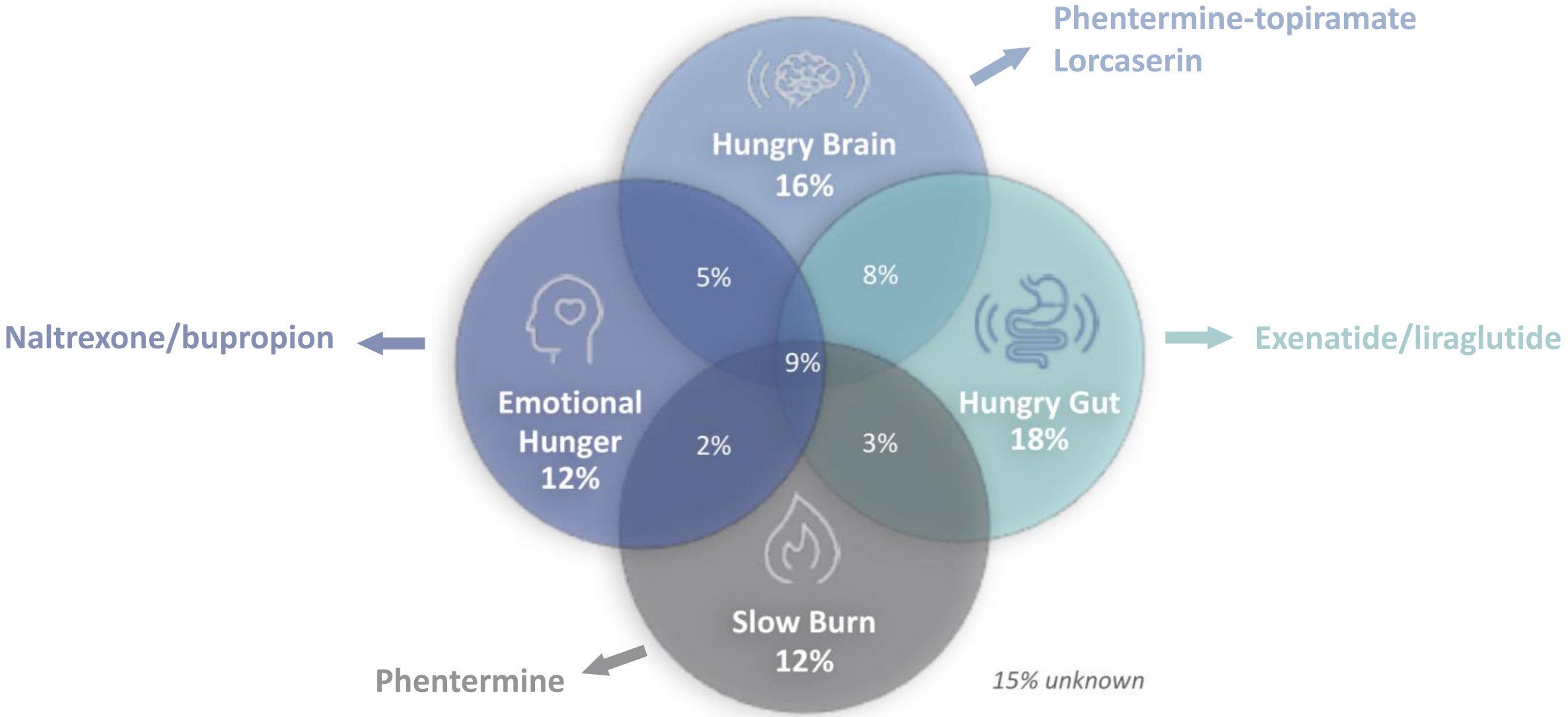
Randomisation (1:1) — Event driven

Key endpoints

Primary: Time from randomisation to first occurrence of MACE

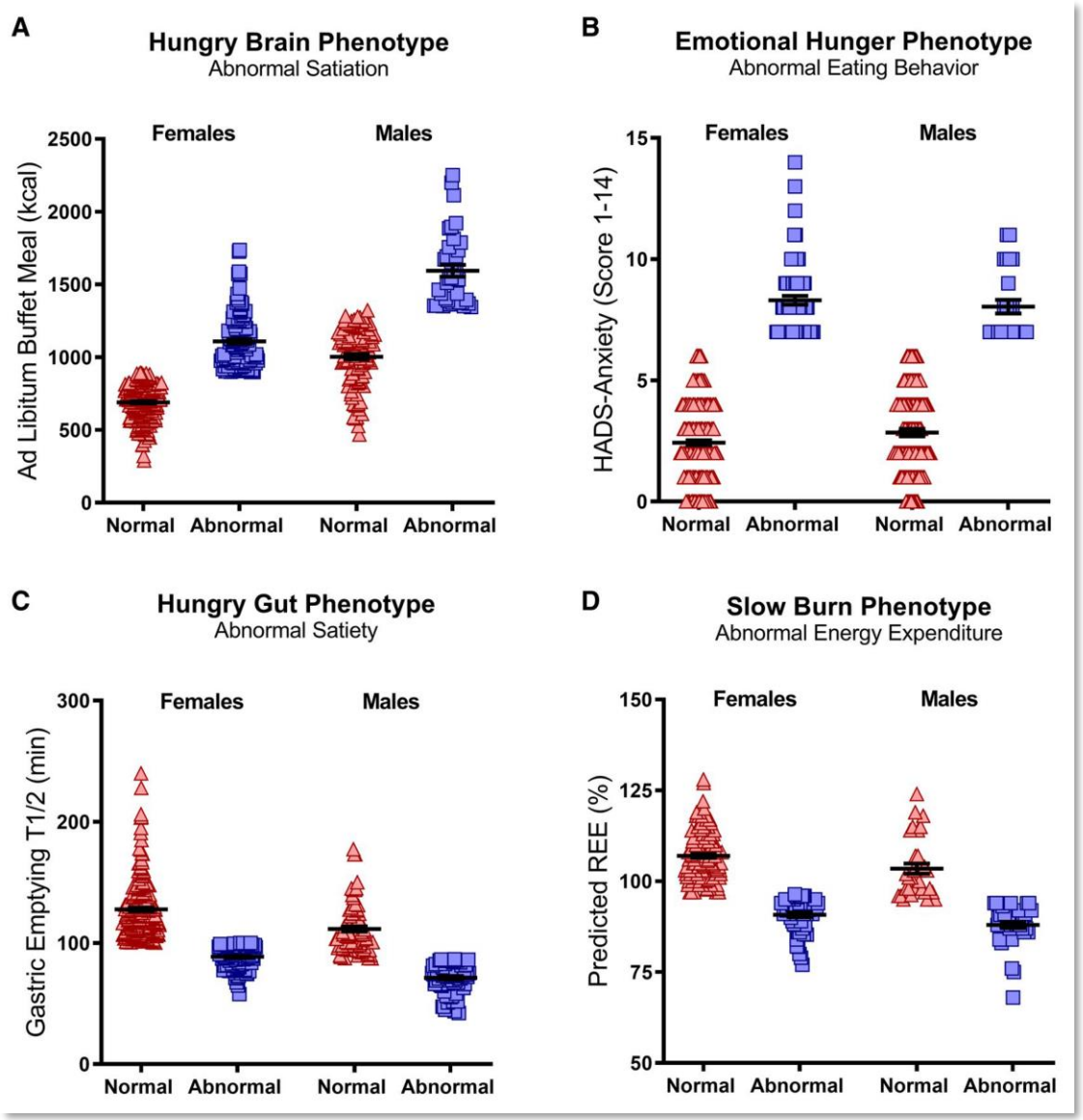
Secondary: Time from randomisation to CV death or all-cause death

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic



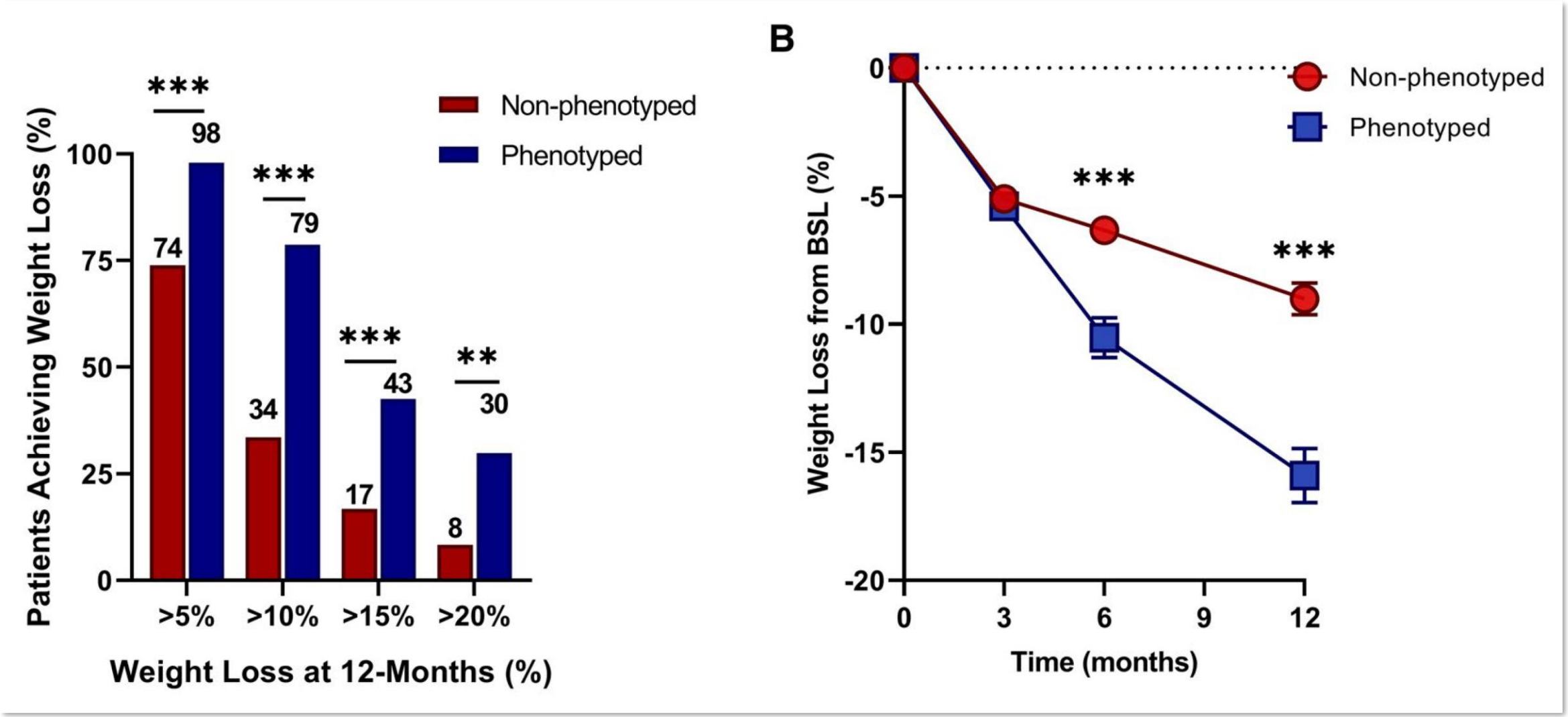
Acosta A et al, Obesity 2021

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic



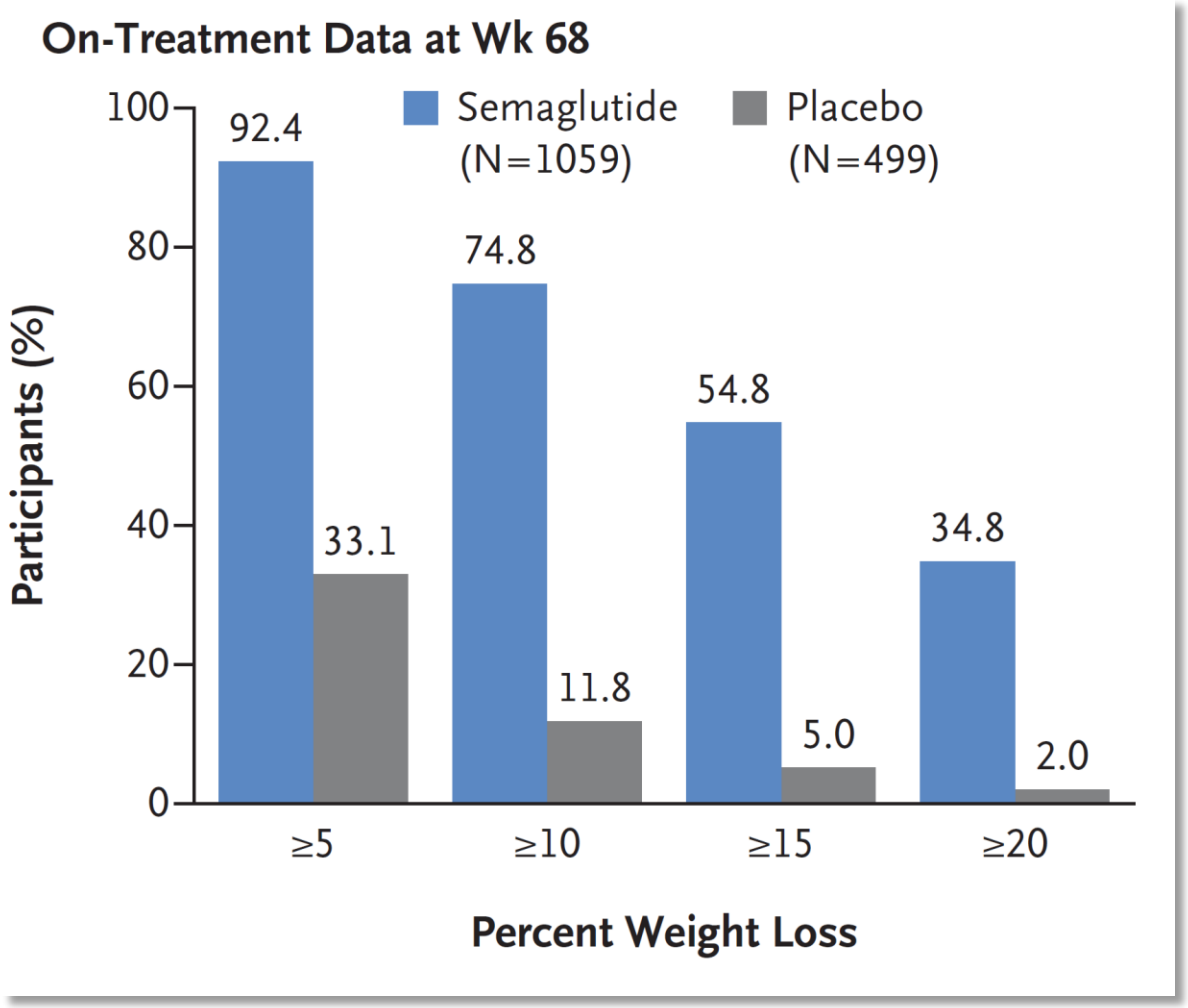
Acosta A et al, Obesity 2021

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic



Acosta A et al, Obesity 2021

ONCE-WEEKLY SEMAGLUTIDE (2.4 MG) IN ADULTS WITH OVERWEIGHT OR OBESITY *(STEP1)*



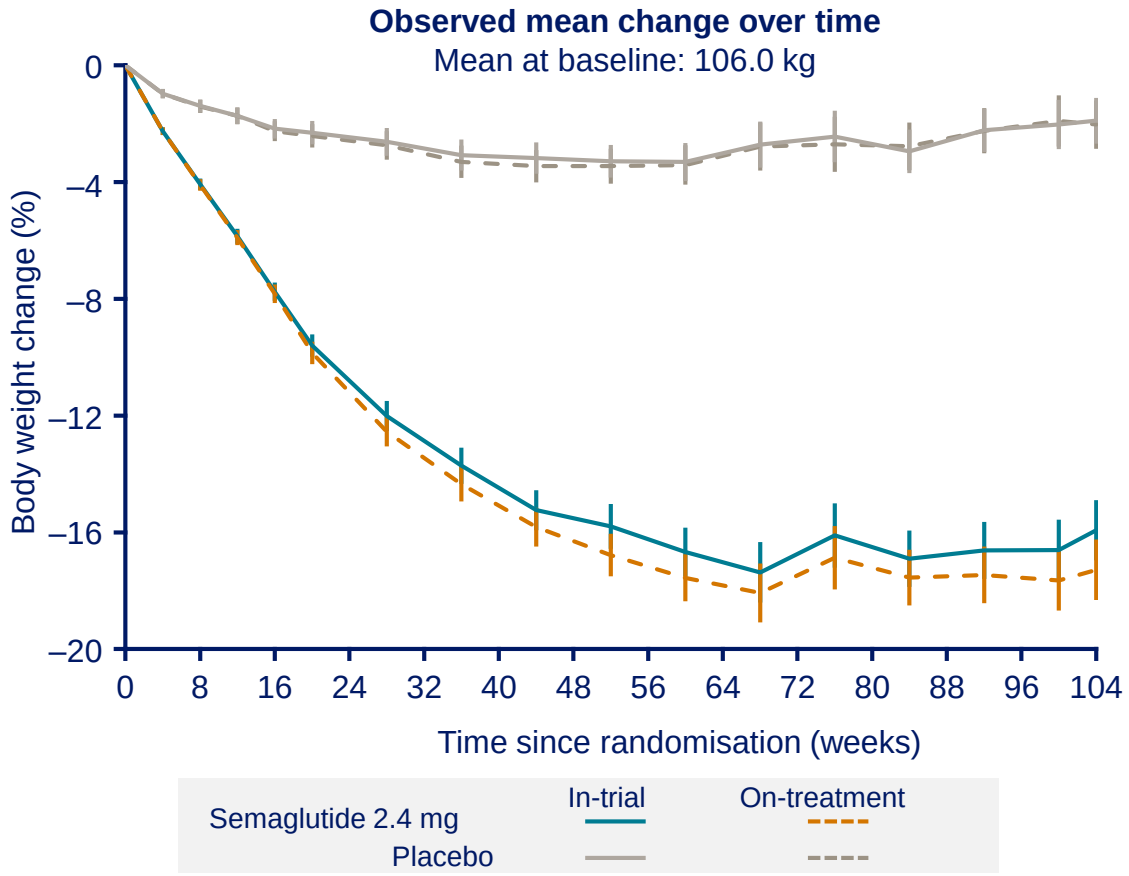
Wilding JPH et al, NEJM 2021

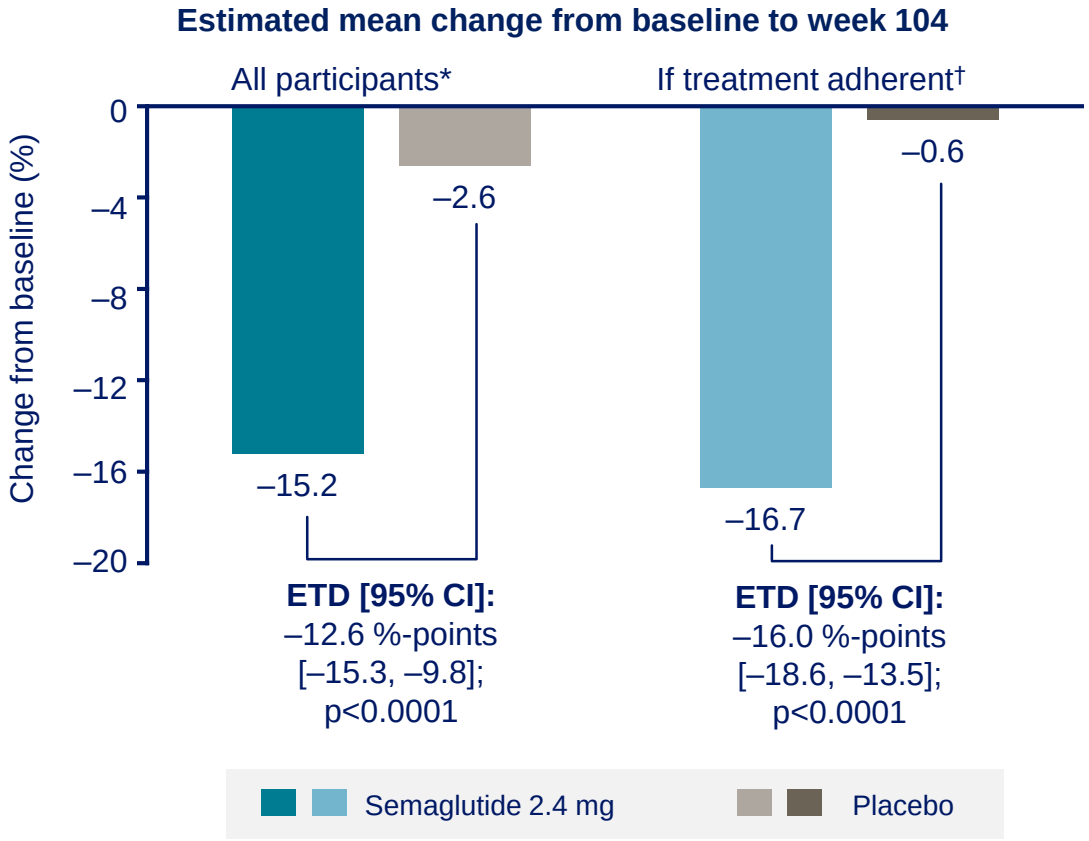
Treatment guidelines are molded by pharmacologic advancements

- Treatment guidelines are molded by the development of new drugs with new MoA.
- We are experiencing, in the filed of obesity, an acceleration in the development of new effective drugs.

Change in body weight with 2 years of semaglutide 2.4 mg

STEP 5 overall population





Semaglutide 2.4 mg is approved in the EU and US for chronic weight management and is under regulatory review in other countries. It may not be approved in your jurisdiction. Please refer to the SmpC approved by the authorities in your country.

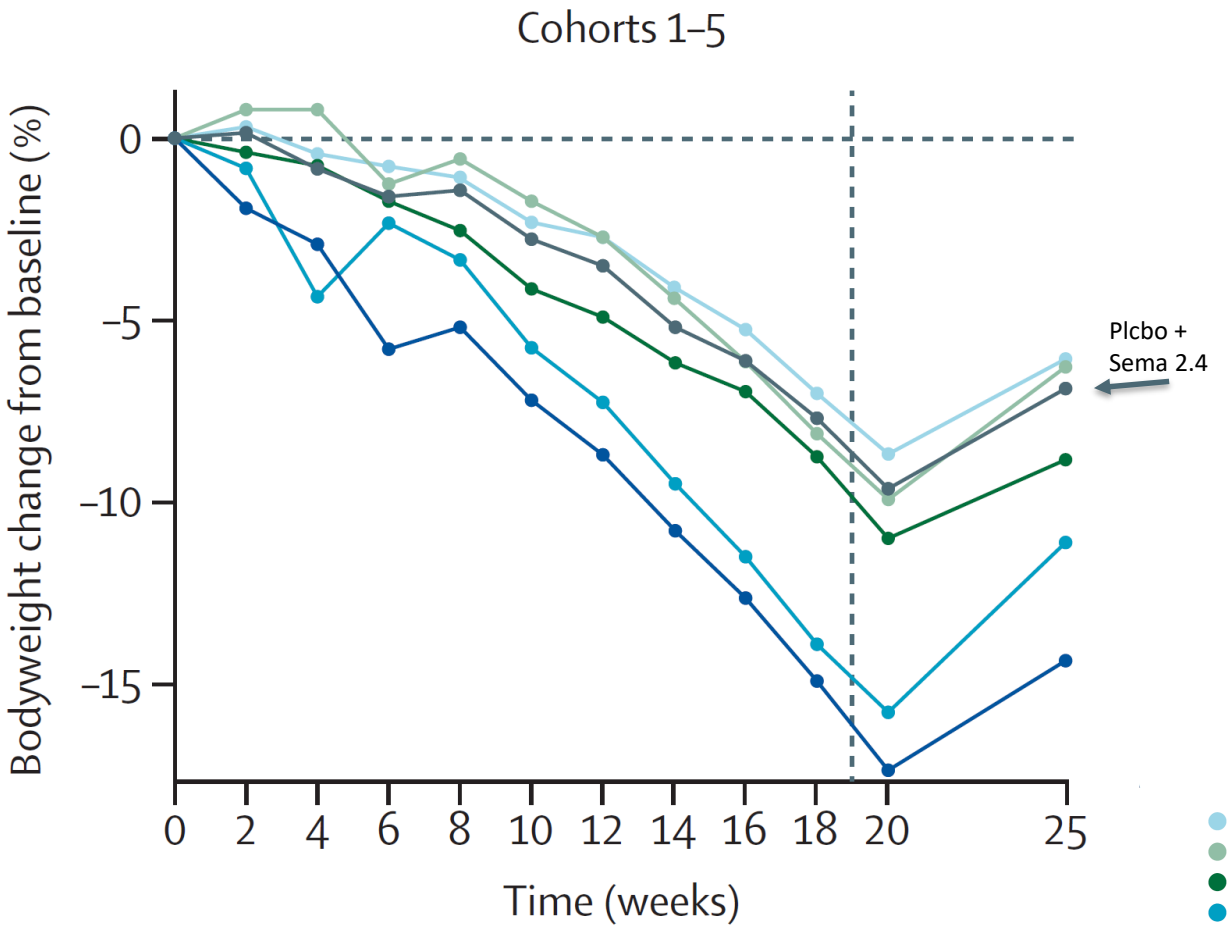
*Treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention); †Trial product estimand (assesses treatment effect if trial product was taken as intended).

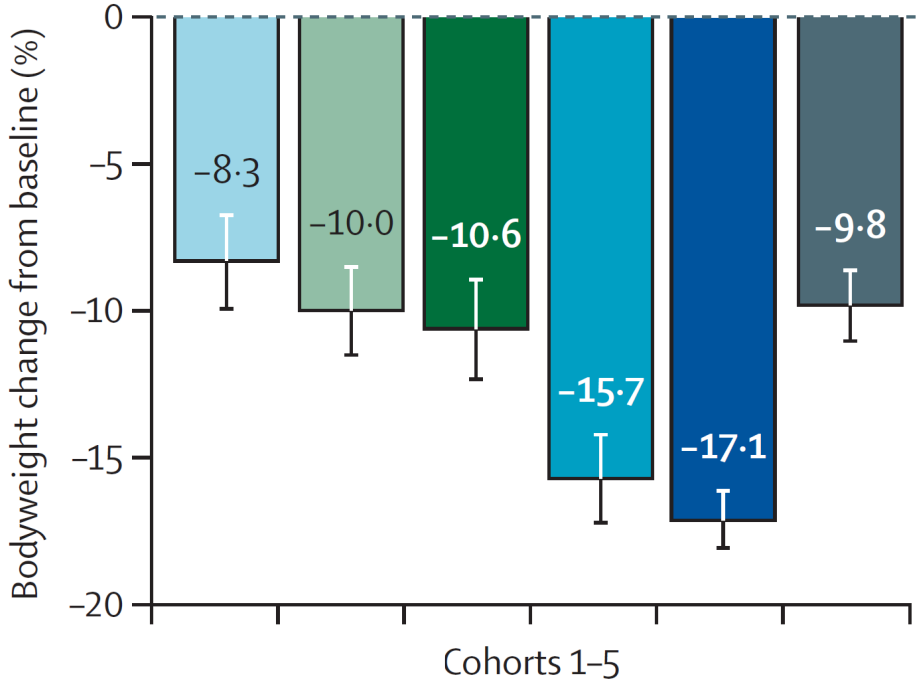
CI, confidence interval; ETD, estimated treatment difference.

Garvey W.T, et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021

SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CONCOMITANT ADMINISTRATION OF MULTIPLE DOSES OF CAGRILINTIDE WITH SEMAGLUTIDE 2·4 mg FOR WEIGHT MANAGEMENT:

A RANDOMISED, CONTROLLED, PHASE 1B TRIAL



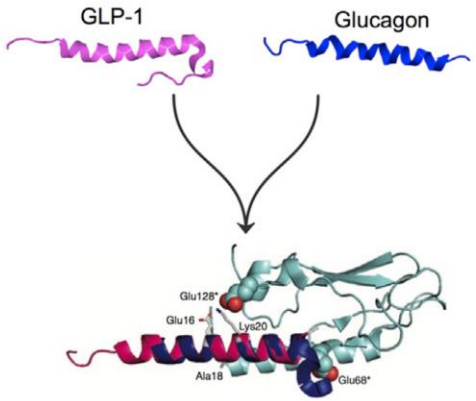


Cagrilintide 0·16 mg plus semaglutide 2·4 mg
Cagrilintide 0·30 mg plus semaglutide 2·4 mg
Cagrilintide 0·60 mg plus semaglutide 2·4 mg
Cagrilintide 1·2 mg plus semaglutide 2·4 mg
Cagrilintide 2·4 mg plus semaglutide 2·4 mg
Pooled placebo plus semaglutide 2·4 mg

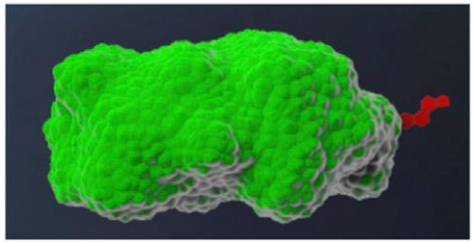
Cohorts 1–5

Enebo et al, Lancet, 2021

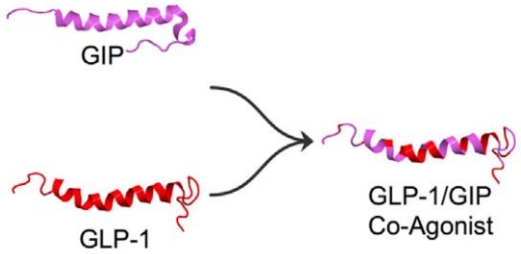
Pro-Glucagon Incretins as a Privileged Pharmacophore



GLP-1/Glucagon Co-Agonist



Targeted Nuclear Hormone Delivery

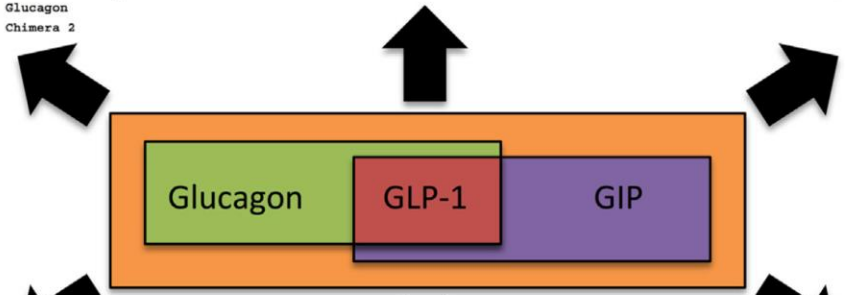


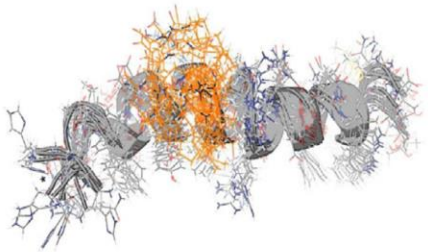
$H^1AEGT^5FTSDV^{10}SSYLE^{15}GQAAK^{20}EFIAW^{25}LVKGR\text{-}NH_2$ GLP-1(1-30)-NH_2

$H^1SQGT^5FTSDY^{10}SKYLD^{15}SRRAQ^{20}DFVQW^{25}LMNT$ Glucagon

$H^1SQGT^5FTSDY^{10}SKYLD^{15}EQAAK^{20}EFIAW^{25}LMNT\text{-}NH_2$ Chimera 2

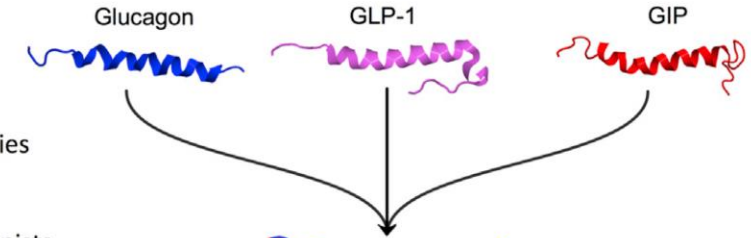
GIP YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-OH
GLP-1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG-OH
Co-Agonist YXEGTFTSDYSIYLDKQAAXEFVNWLLAGGPSSGAPPPSK-NH_2





Alternative Combinations & Chemistries

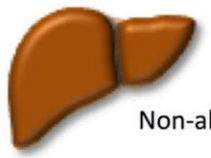
- Adjunctive Protein Therapy
- Selective Antagonists
- Mixed Reciprocal Agonists/Antagonists
- Peptide-Friendly Pro Drugs
- Lipid-based Peptide Stapling



Glucagon/GLP-1/GIP
Tri-Agonist

Alternative Disease Indications

Neurodegenerative Diseases
Depression

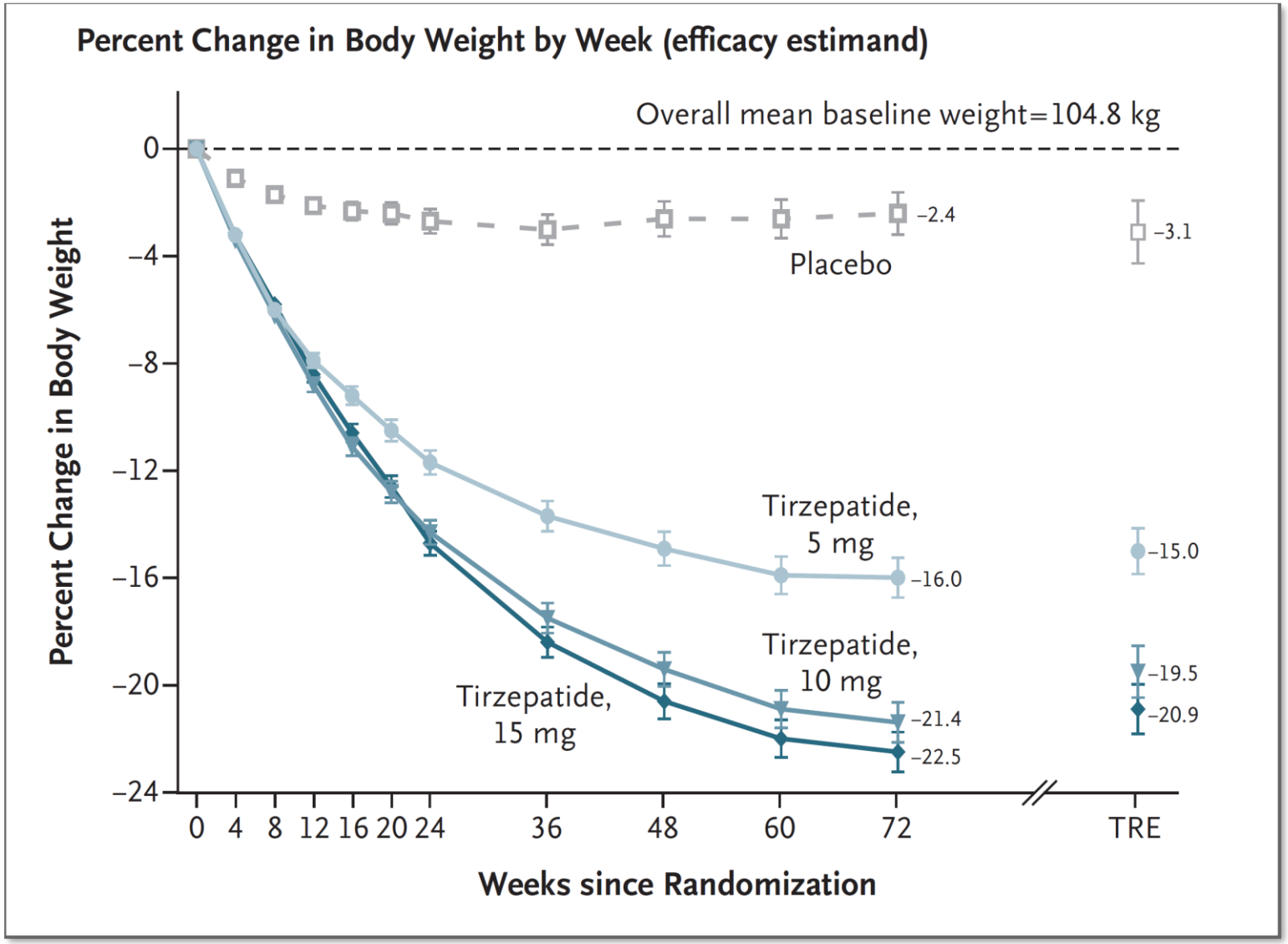


Non-alcoholic Steatohepatitis

Tschop M, Cell Metab 2016

Tirzepatide Once Weekly for the Treatment of Obesity

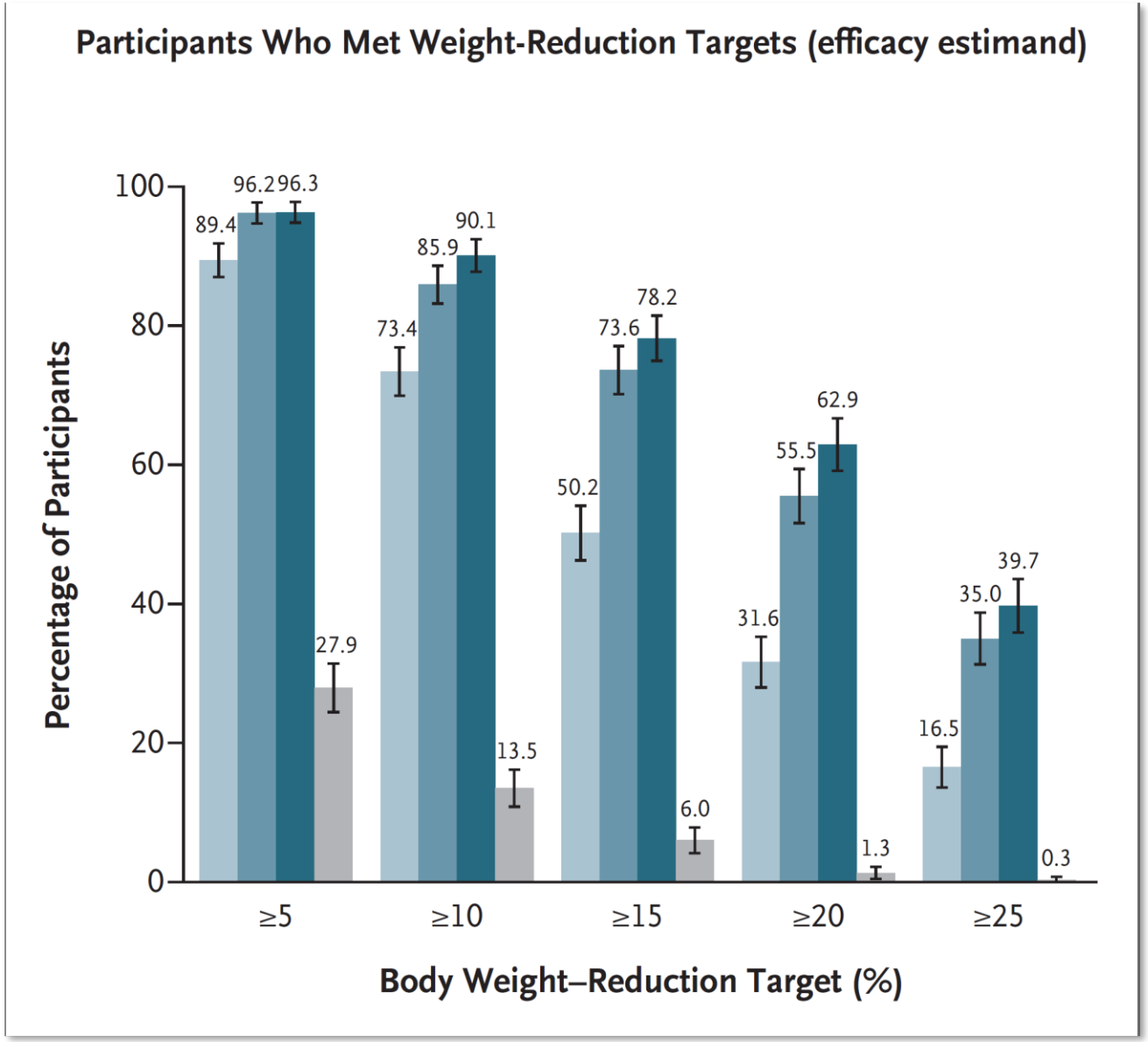
SURMOUNT-1



Jastreboff AM et al, NEJM 2022

Tirzepatide Once Weekly for the Treatment of Obesity

SURMOUNT-1



Jastreboff AM et al, NEJM 2022

Proportionality in obesity management