Obesity in people living with HIV

Why and how do we combat overweight and CV risk?

Prof. Dr. Robert Hilbrands

Endocrinologist & Nephrologist

Universitair Ziekenhuis Brussel

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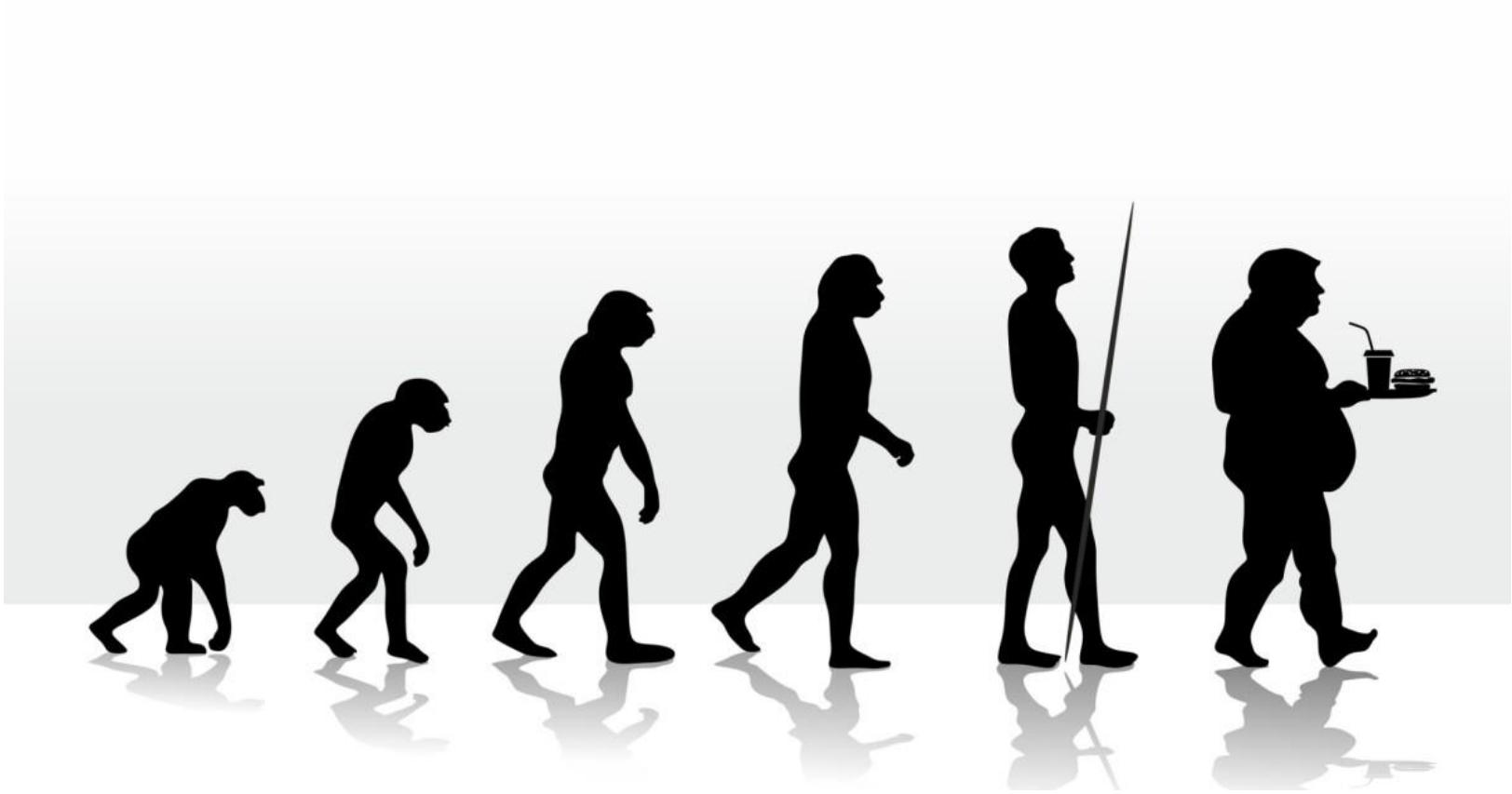
The obesogenic environment



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Obesity in Belgium

- Mean BMI adult population (>18 years): **26,6**
- Percentage adult population with overweight (BMI ≥ 25): **49%**
- Percentage adult population with obesity (BMI ≥ 30): **18%**

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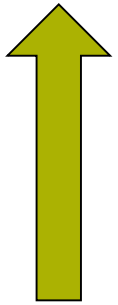
Sciensano 2024

Obesity is a risk factor for cardiovascular disease

Cardiometabolic syndrome

1. Overweight and obesity
2. Hypertension
3. Dyslipidemia
4. Type 2 diabetes/prediabetes



Cardiovascular disease (AMI, CVA)
Renal disease
MORTALITY

BMI cutoffs differ by ethnic populations

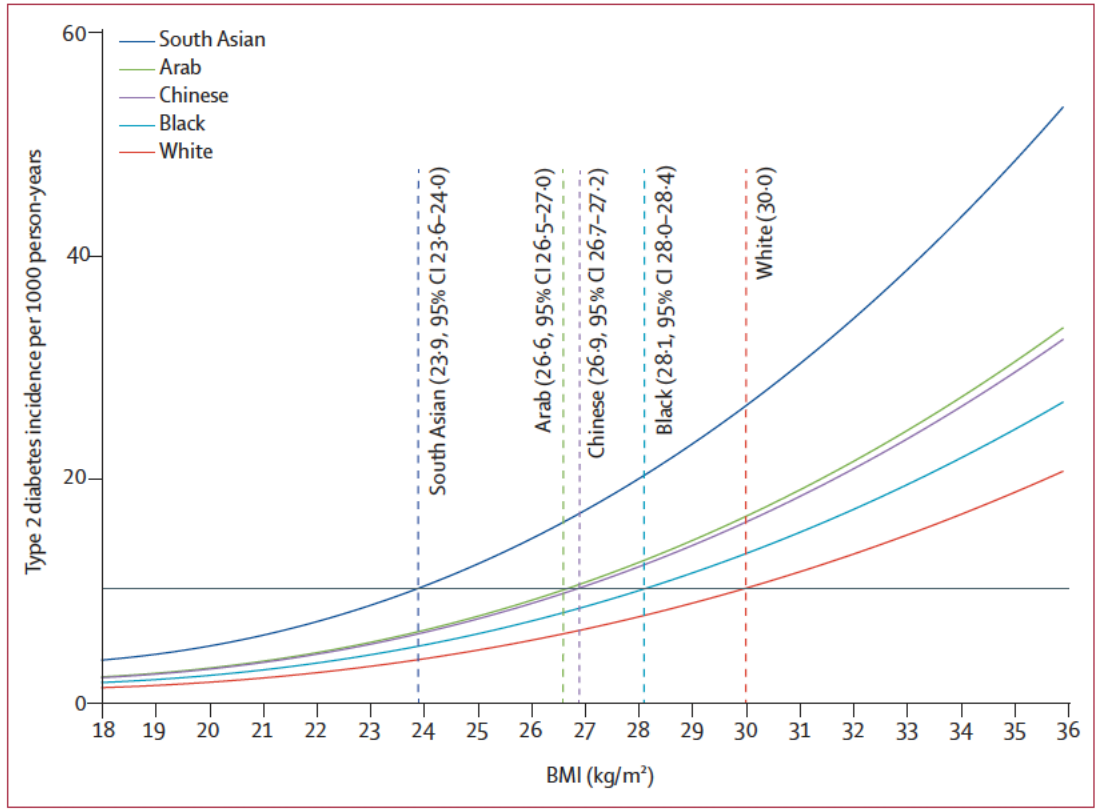


Figure 2: **Age-adjusted and sex-adjusted BMI cutoffs in minority ethnic populations in England equivalent to a BMI cutoff of 30·0 kg/m² in White populations in relation to type 2 diabetes incidence**
The incidence of type 2 diabetes for a BMI of 30·0 kg/m² in the White population can be read off the graph at the intersection of the grey horizontal line and the fitted line for the White population.

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Caleyachetty R et al. Lancet Diab Endo 2021, p419

Waist circumference is a better predictor of metabolic risk

Central/abdominal obesity

↓

Increased abdominal visceral fat

↓

Increased insulin resistance

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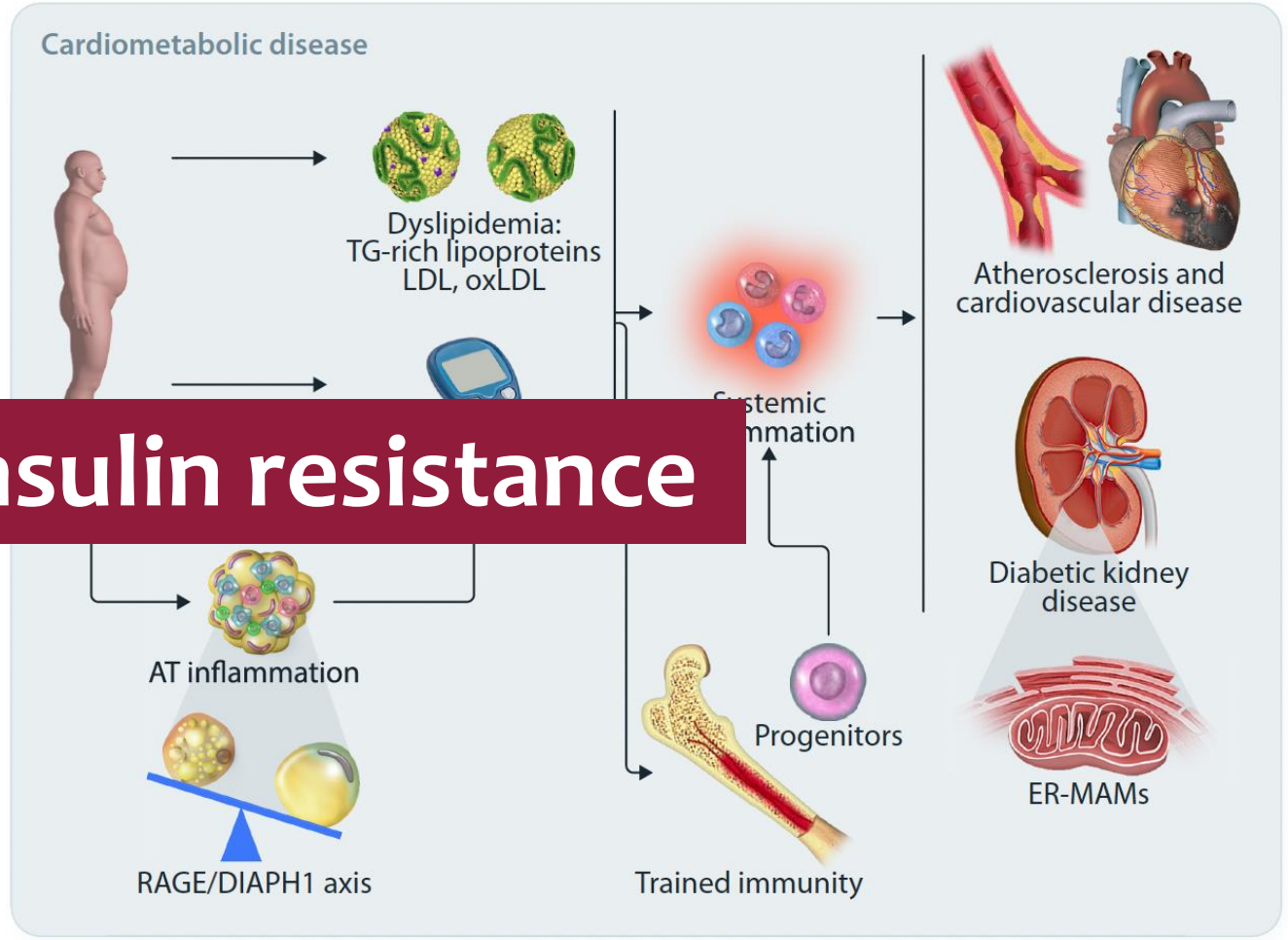
Pathofysiology of cardiometabolic disease – insulin resistance



AT: adipose tissue inflammation

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Chavakis et al. Cardiovasc research 2023, p2771

Obesity-associated metabolic disturbances

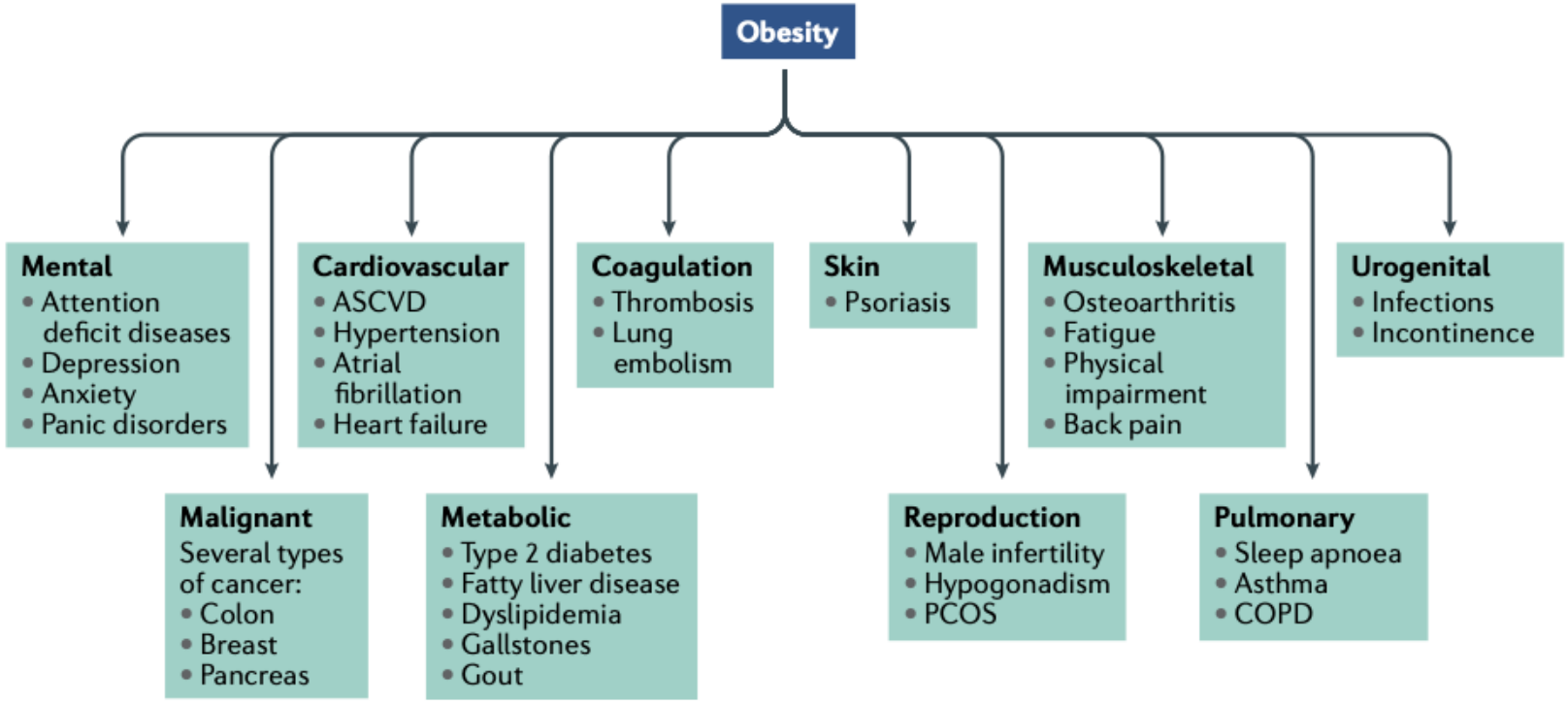


Fig. 1 | **Obesity-associated metabolic disturbances.** Most prominent metabolic and psychological comorbidities associated with morbid obesity. ASVCD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; PCOS, polycystic ovary syndrome.

Müller T et al. Nat Rev Drug discovery 2021

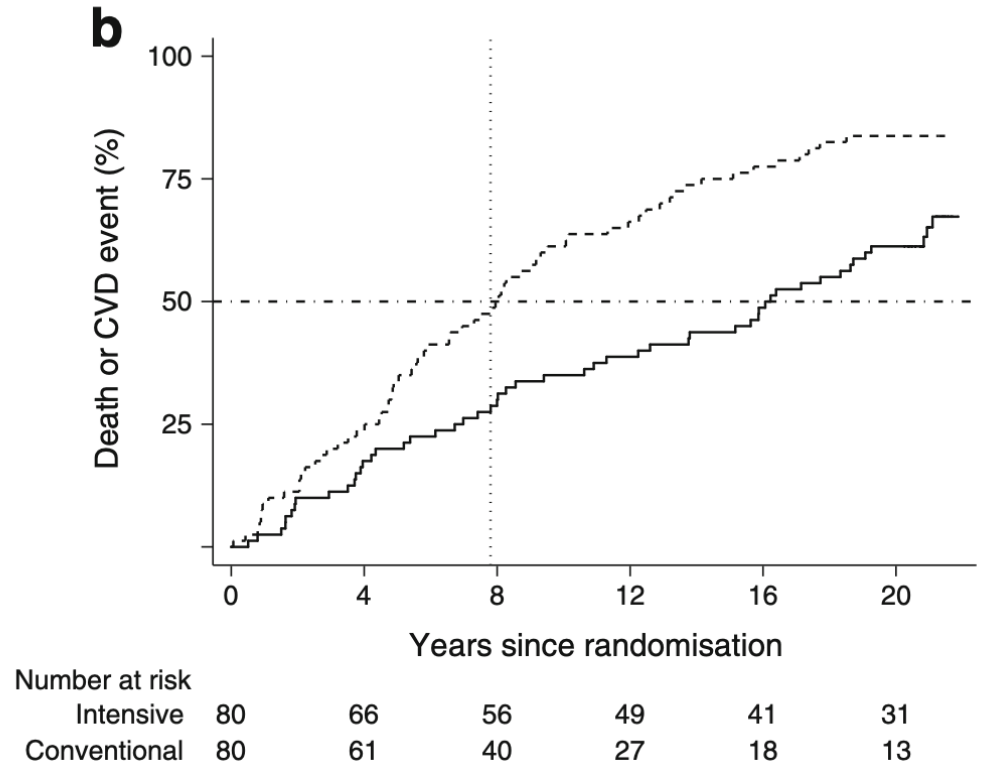
Management and CV risk reduction

Management of cardiometabolic syndrome is **multifactorial**

7.9 years survival benefit when all risk factors are under control

Control all in T2D patients:

- HbA1c <6.5/7.0%
- **Cholesterol**
- **Fasted triglycerides <150 mg/dL**
- **Systolic BP <130 mmHg**
- **Diastolic BP <80 mmHg**
- Smoking cesation
- Life-style changes
- Physical activity



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Gaede et al. Diabetologia 2016, p2298

Obesity – Goals of care

- Health gain → reduce CV risk and mortality
- **Treatment target** is not necessarily normality but the level where benefits outweigh risks
- Not yet established for obesity but **15% weight loss** is a reasonable starting point

Lingvay et al. Lancet 2024, p972

Management of obesity

- Life-style interventions
- Pharmacotherapy
- Bariatric surgery

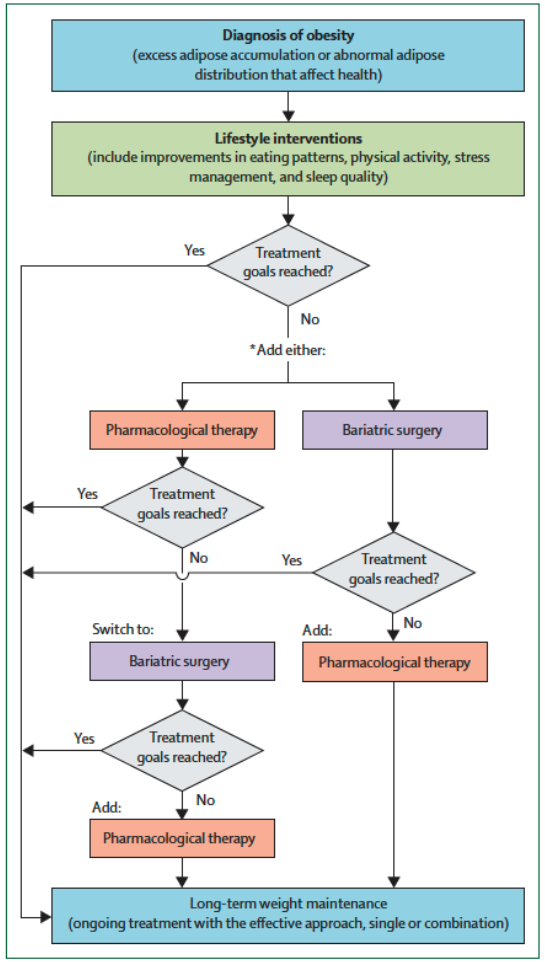

Figure 2: **Conceptual approach to the treatment of obesity**
*For individuals with severe disease (as defined by either very high BMI or presence of severe obesity-related co-morbidities) combination approach with lifestyle interventions and either pharmacological therapy or bariatric surgery should be considered first line, as appropriate.

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Lingvay et al. Lancet 2024, p972

Life-style interventions

Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Claudia-Martina Messow, Naveed Sattar, Roy Taylor**

Lancet Diabetes Endocrinol 2019

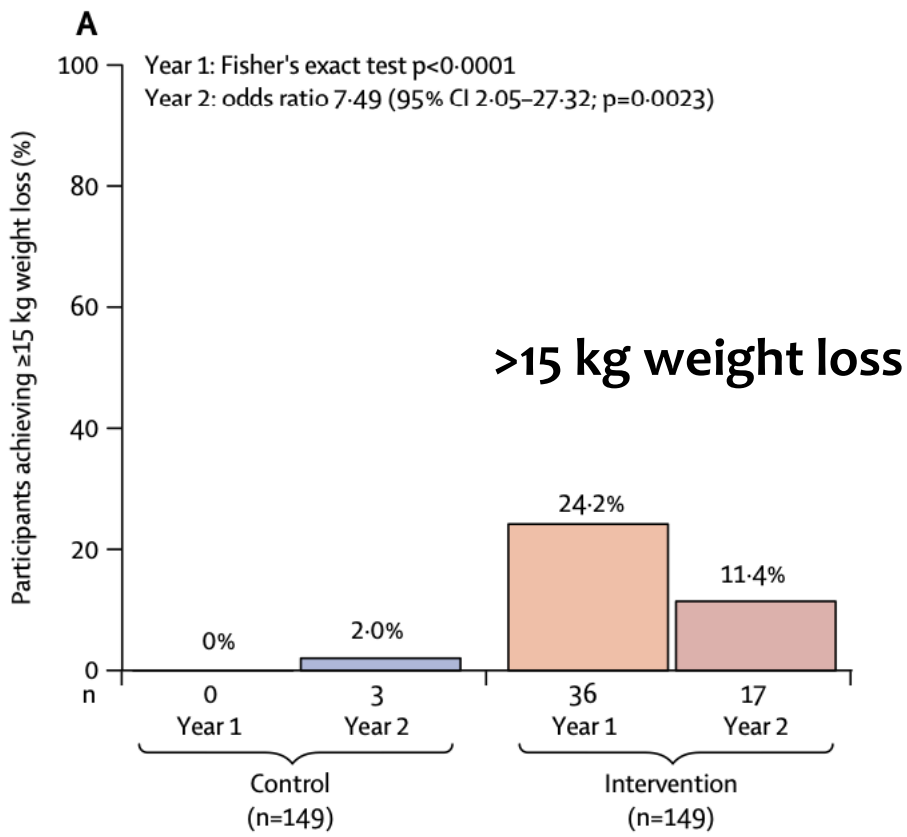
Population:

- Type 2 diabetes 0-6 year from diagnosis
- 20-65 years
- BMI 27-45 kg/m^2 (mean BMI 35, mean BW 100 kg)

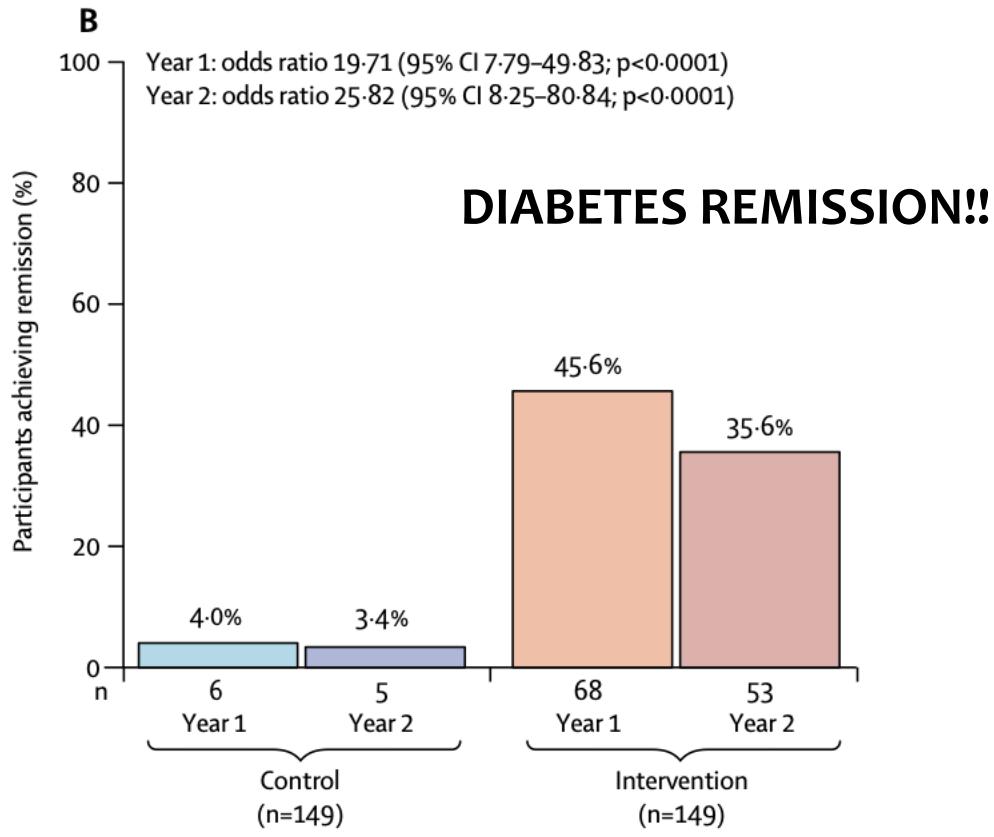
Intervention

- Stop all antidiabetic drugs, AHT drugs
- Total diet replacement (850 kcal/d 12-20 weeks)
- Stepped food re-introduction (2-8 weeks)
- Structured support for weightloss maintenance

Weight loss >15% achievable but only in a minority



>15 kg weight loss



DIABETES REMISSION!!

21% early withdrawal from study
Main reason: social

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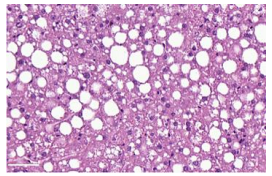
PROGRESSIVE WEIGHT LOSS HAS DOSE-DEPENDENT AND TISSUE-DEPENDENT BIOLOGICAL EFFECTS

Benefits of 16% weight loss

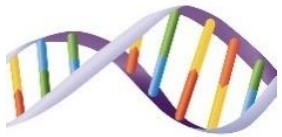
Liver insulin sensitivity



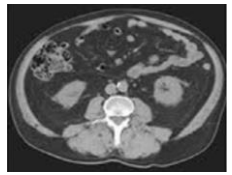
Liver triglycerides

β-cell function

Muscle insulin sensitivity

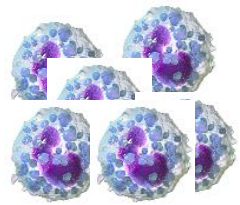


Gene expression in s.c. adipose



Abdominal adipose tissue

Adipose insulin sensitivity



Inflammatory markers

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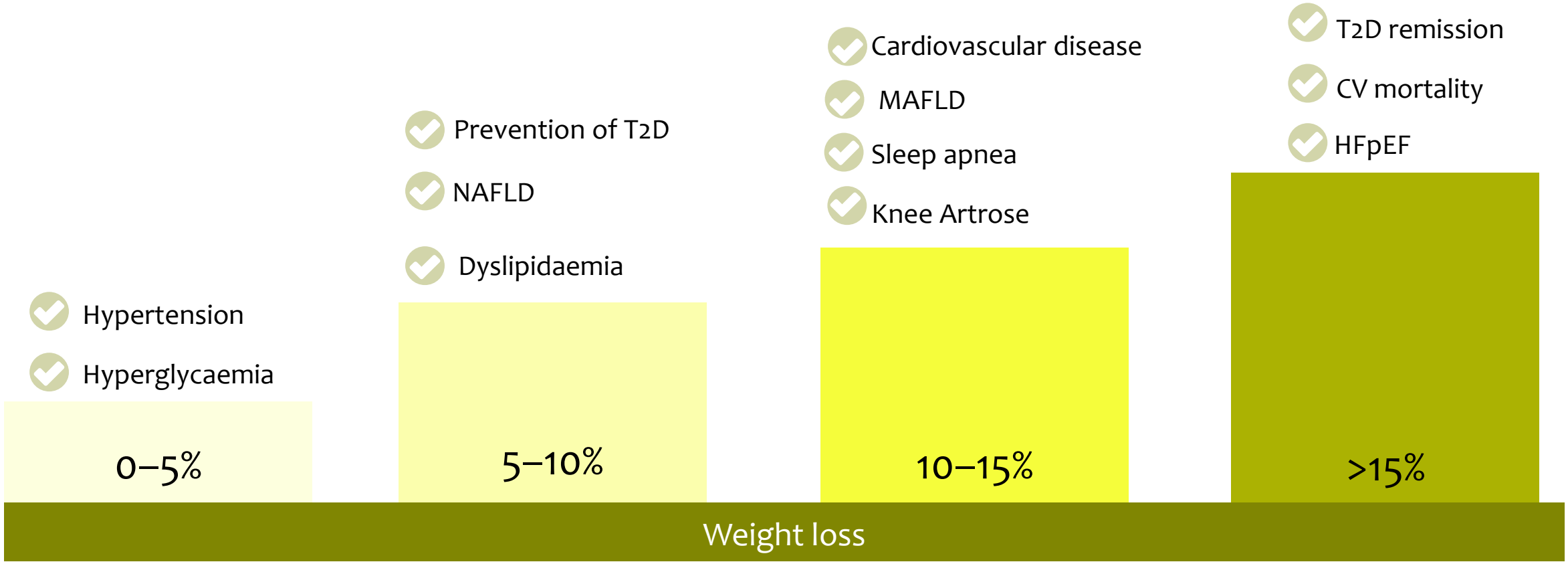
Magkos F et al. Cell Metabolism 2016;23:591–601.

How much weight loss is needed?

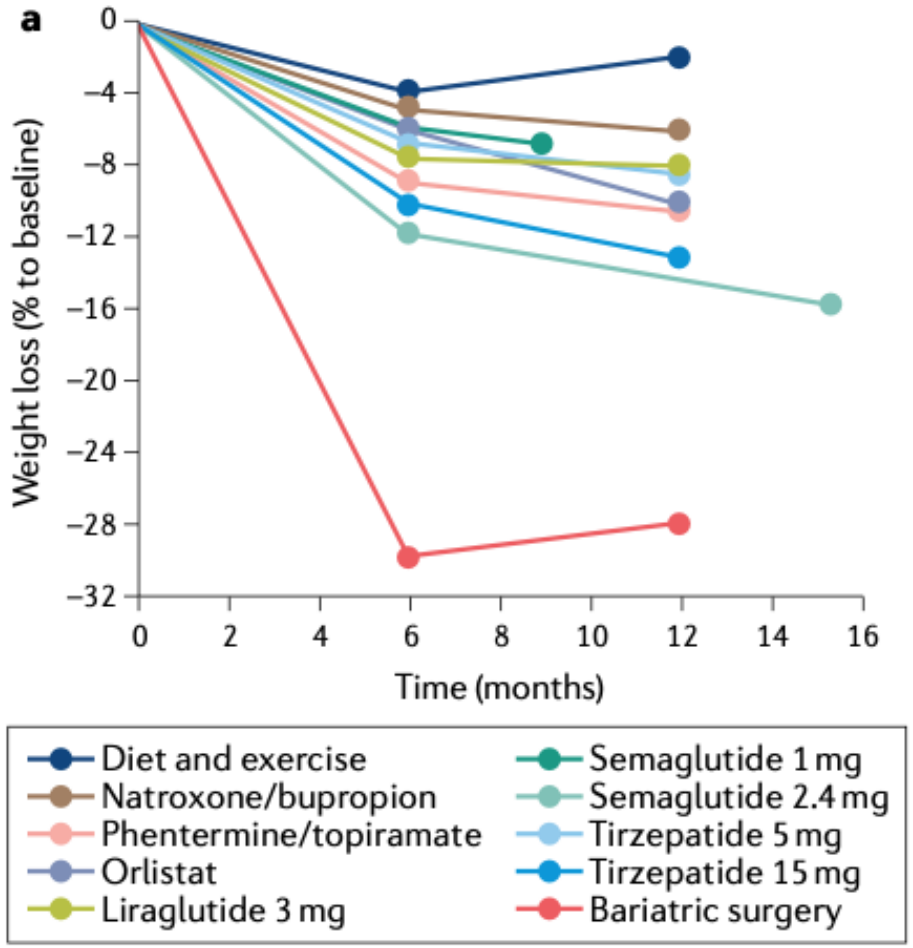


CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSAS, obstructive sleep apnoea syndrome; TG, triglycerides.
Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–51;
Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85.

Pharmacotherapy for obesity

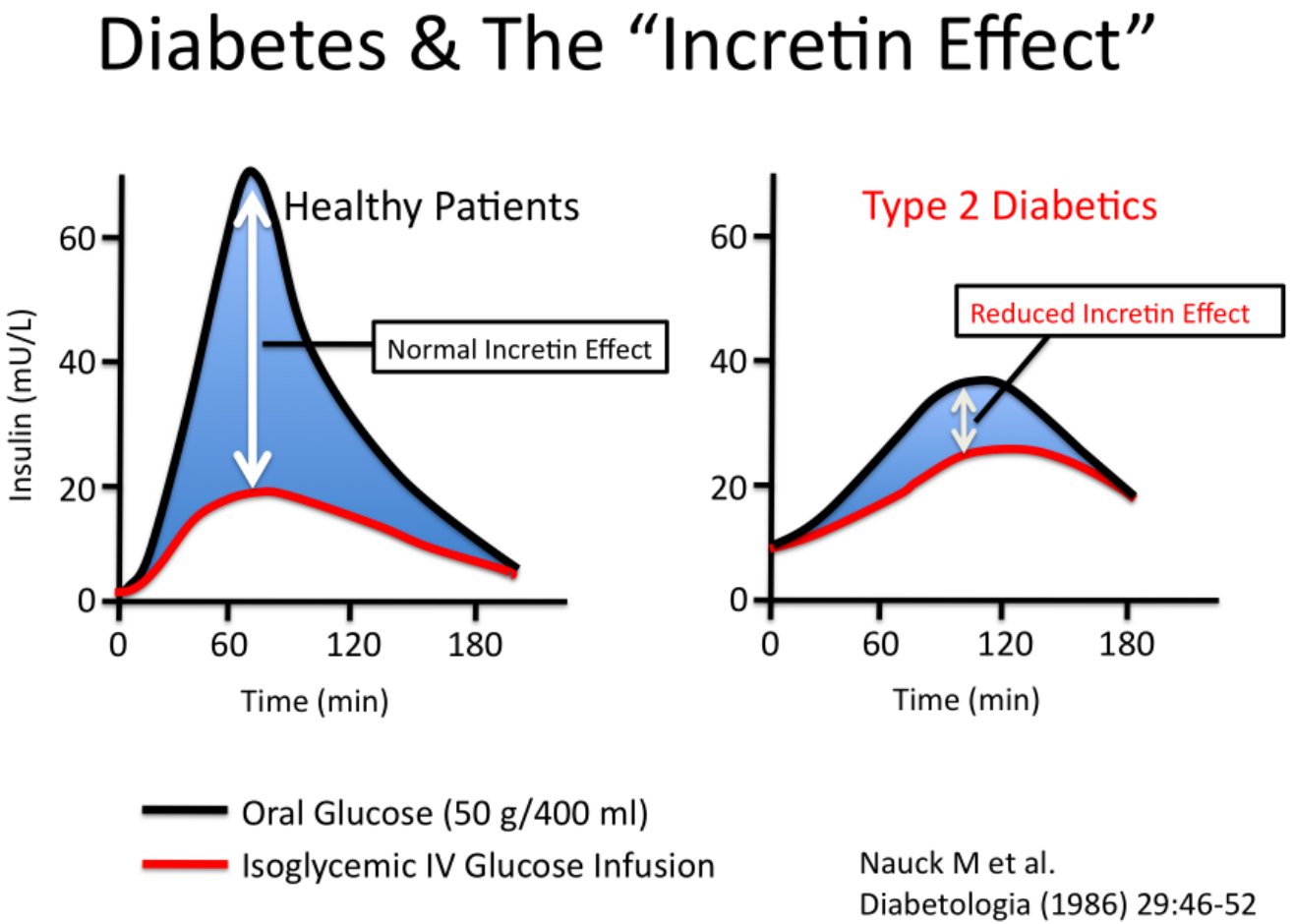
- Orlistat
- Liraglutide
- Naltrexone plus bupropion
- Phentermine plus topiramate (not in Belgium)

Safe and effective providing 5-10% weight loss if patient responds



Müller T et al. Nat Rev Drug discovery 2021

GLP-1 receptor agonists: Incretin effect



Nauck M et al.
Diabetologia (1986) 29:46-52

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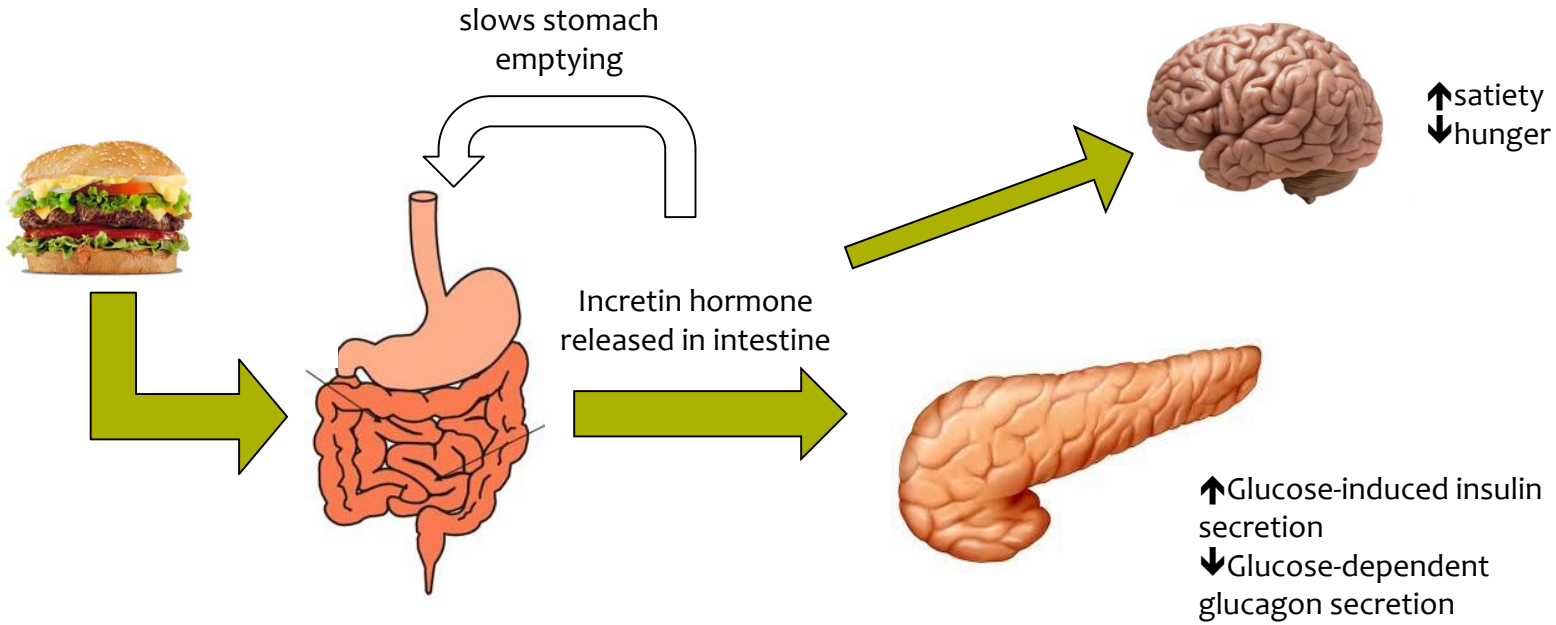
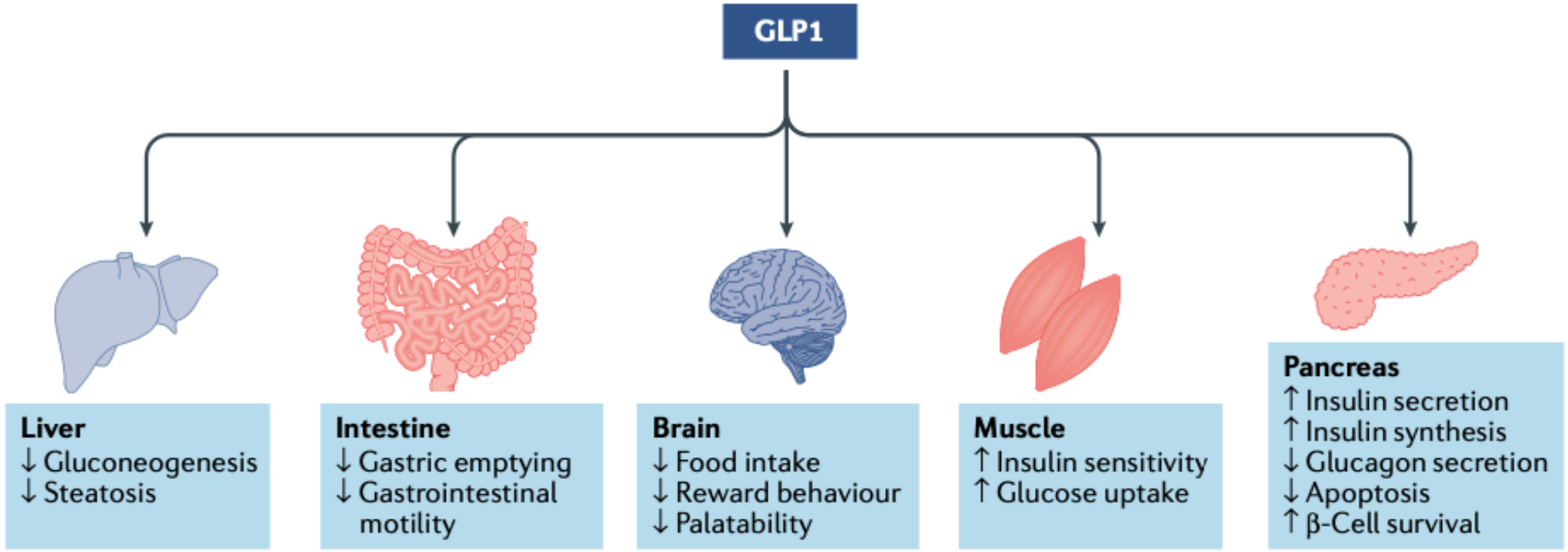
Incretines

- **Glucagon-like peptide (GLP-1)**
- **Glucose-dependent insulinotropic peptide (GIP)**



<u>Glucose-dependent</u> effects!!

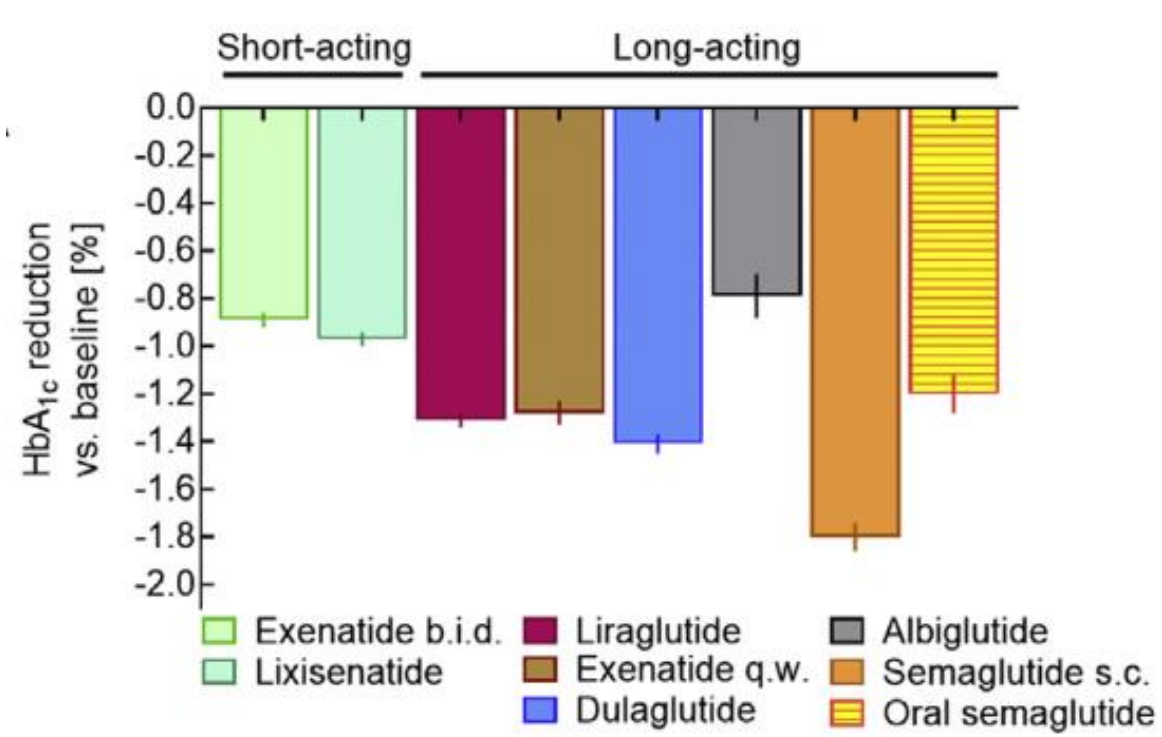
Effects of GLP1 receptor agonism on energy and glucose metabolism



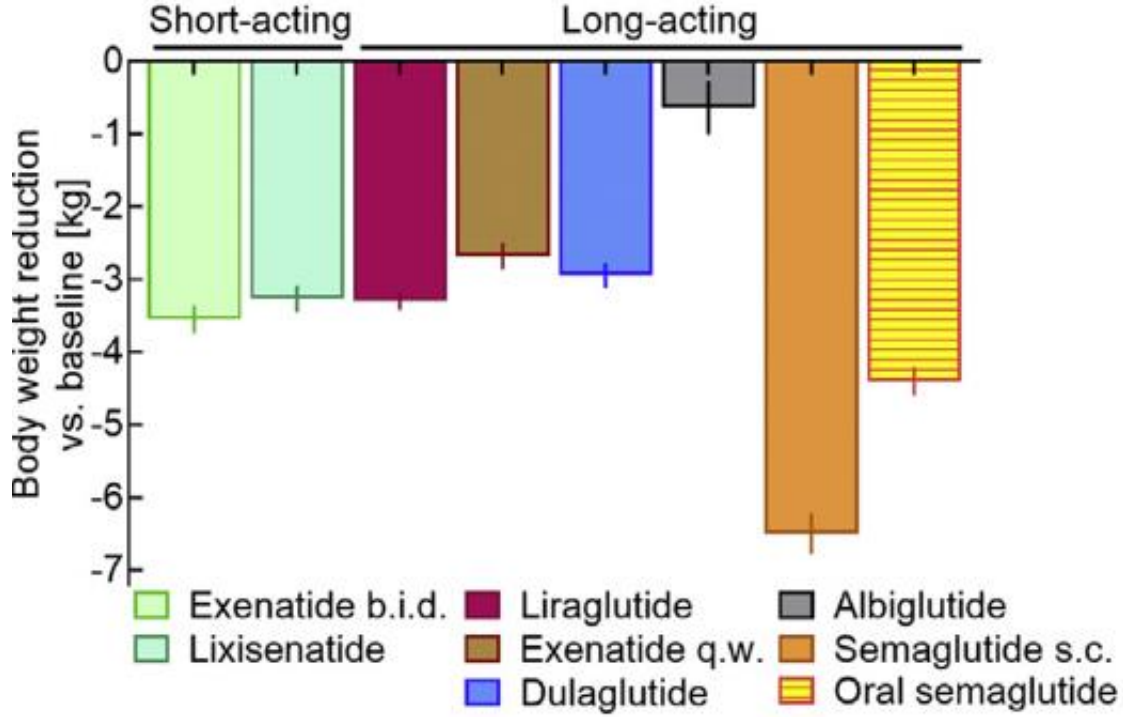
Müller T et al. Nat Rev Drug discovery 2021

GLP-1 RA in Type 2 diabetes

Lowering HbA1c



Weight loss



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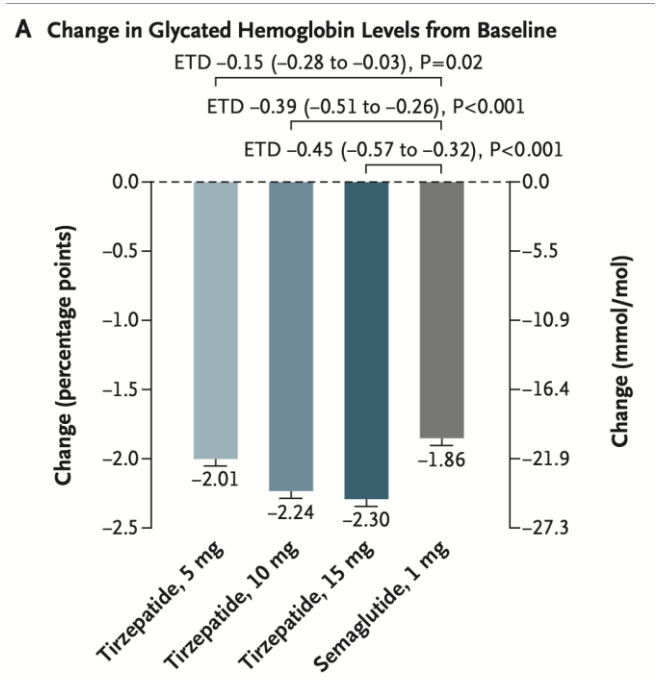
Nauck M et al. Molecular Metabolism 2021

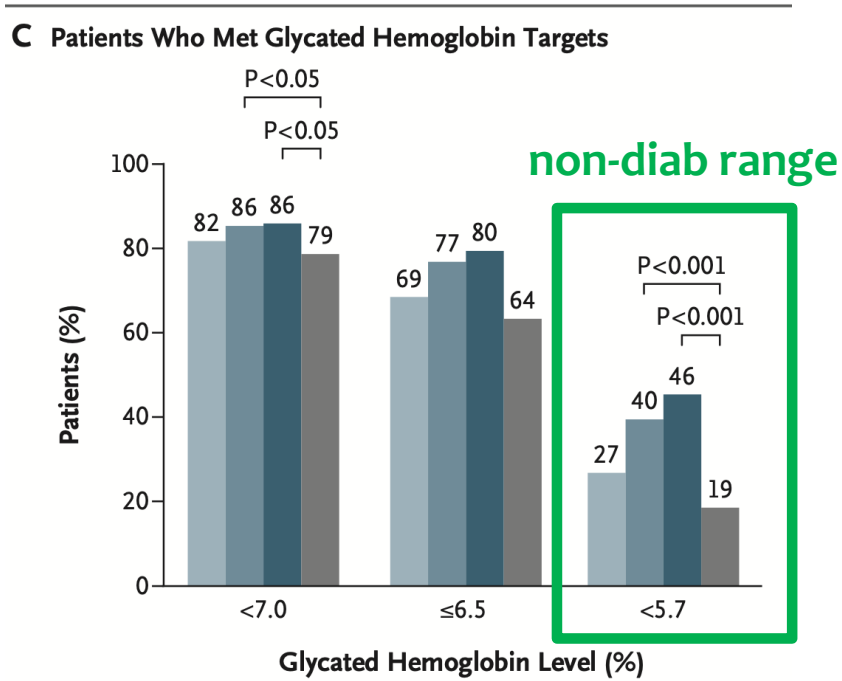
GLP-1/GIP RA and **diabetes**: SURPASS 2 (Tirzepatide)

HbA1c at 40 weeks

Add on to metformin vs sema

- Baseline HbA1c 8.26%
- Duration diab 8.6 years
- Bodyweight 93.7 kg
- BMI 34.2 kg/m²





Tirzepatide, 5 mg | Tirzepatide, 10 mg | Tirzepatide, 15 mg | Semaglutide, 1 mg

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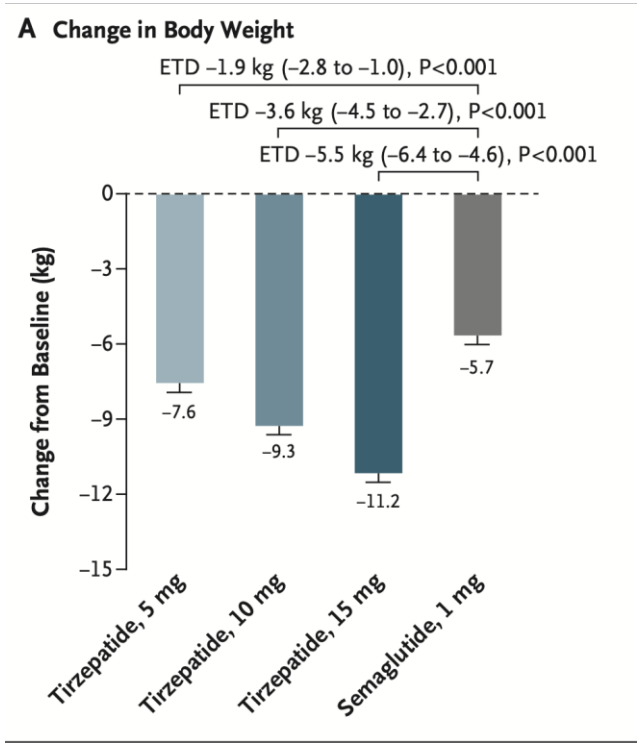
Frias J et al. NEJM 2021, p503

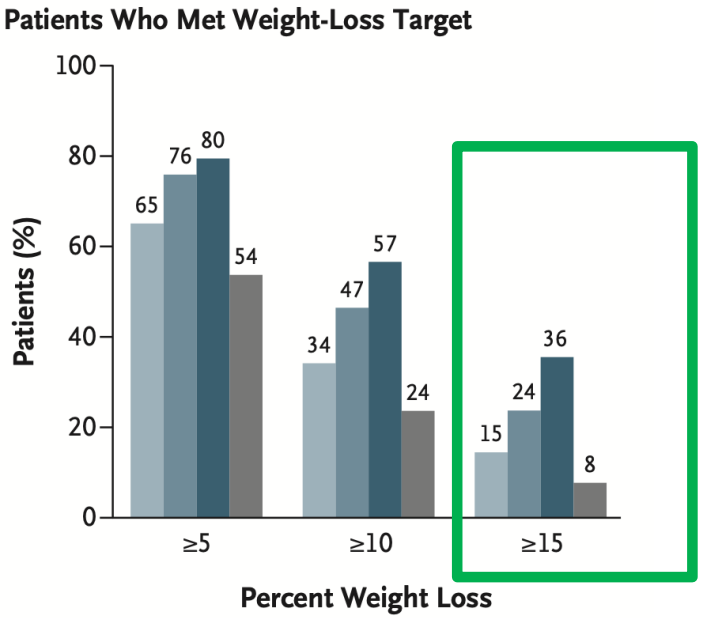
GLP-1/GIP RA and **diabetes**: SURPASS 2 (Tirzepatide)

Weight loss at 40 weeks

Add on to metformin vs sema

- Baseline HbA1c 8.26%
- Duration diab 8.6 years
- Bodyweight 93.7 kg
- BMI 34.2 kg/m²





Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Semaglutide, 1 mg

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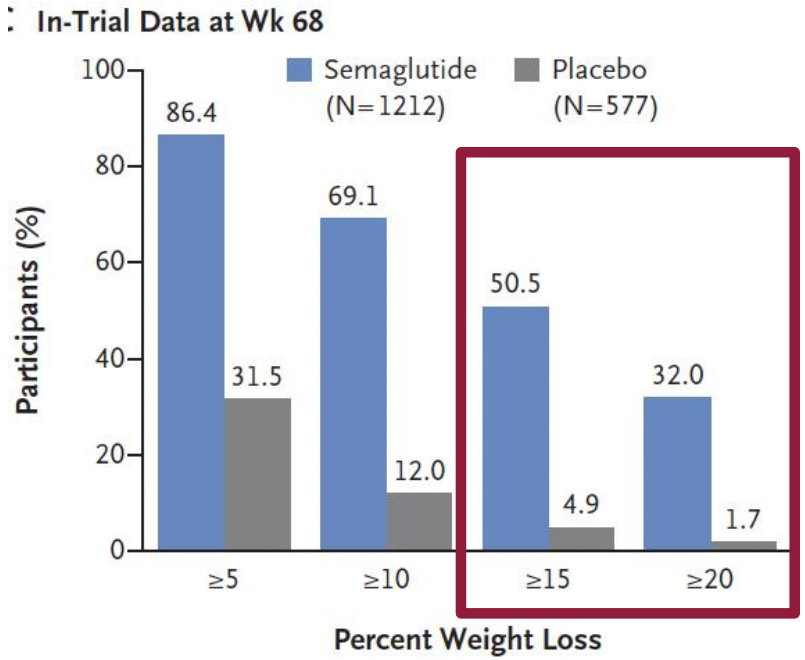
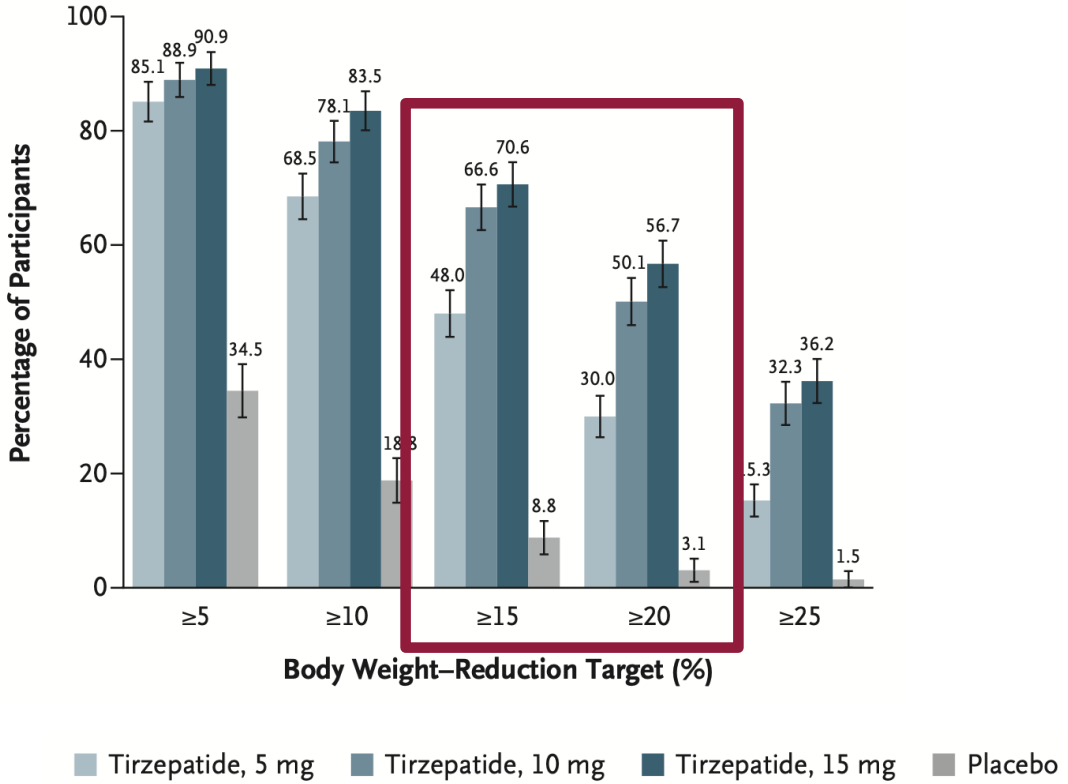
Incretines for obesity without diabetes

Treatment for **obesity without diabetes**: STEP-1 and SURMOUNT-1

Semaglutide 2.4 mg/wk



Tirzepatide



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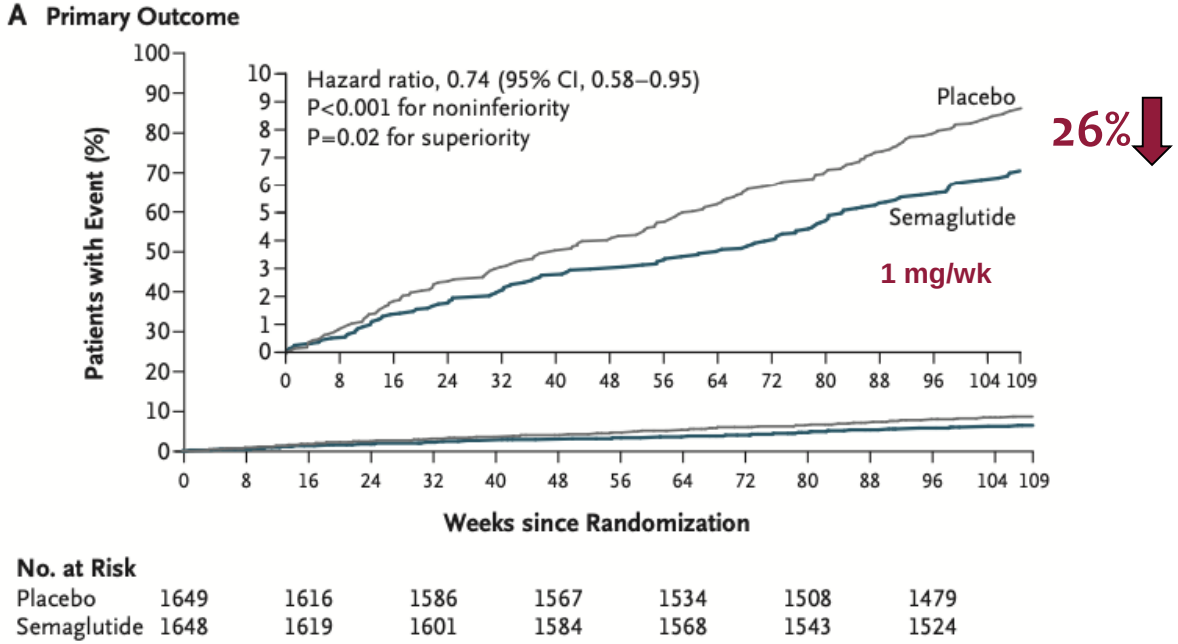
Jastreboff A et al. NEJM 2022, p205

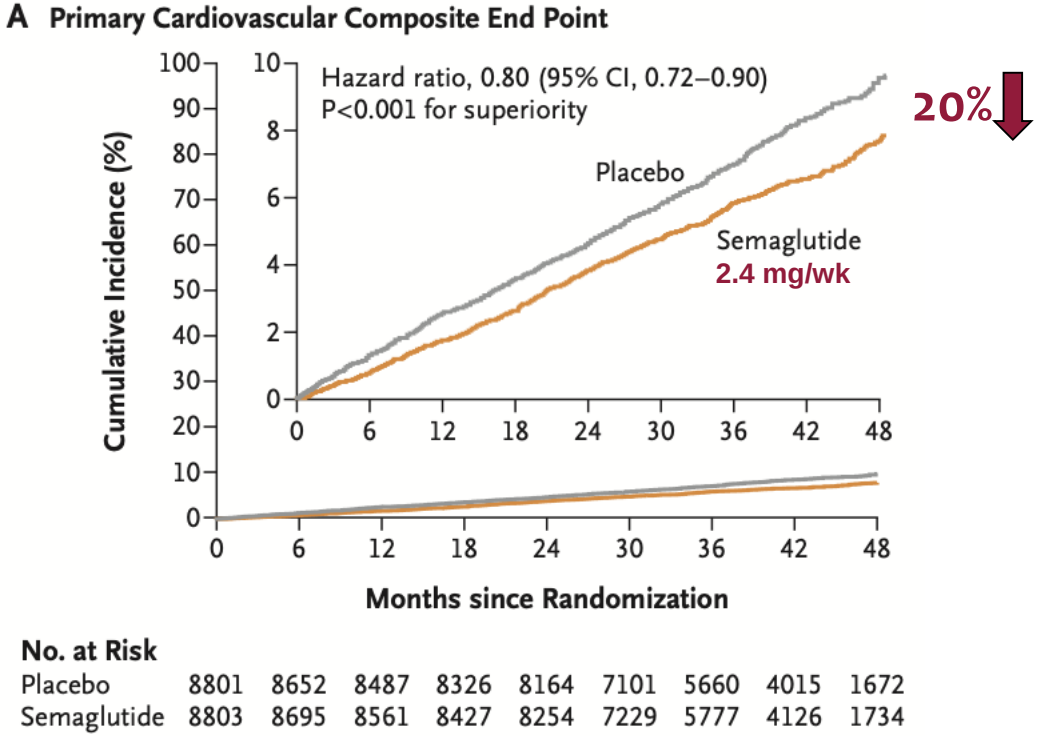
GLP-1 RA reduces CV risk

Composite endpoint: CV death, nonfatal AMI or nonfatal stroke

Type 2 diabetes + CV disease



No diabetes, BMI >27 + CV disease



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Marso S et al. NEJM 2016; Lincoff A et al. NEJM 2023

Semaglutide **1 mg**/week in PLWHIV

- RCT (n=108)
- HIV-1 + lipohypertrophy, no diabetes
- BMI 33 kg/m²; waist circumference 107 cm

- **Primary endpoint:** change at 32 weeks in adipose tissue quantity by body compartment

- **Outcome:** abdominal visceral adipose tissue **-30.6%**

Eckard A et al. Lancet Diabetes Endocrinol 2024, p523

Semaglutide **1 mg**/week in PLWHIV

- Secondary outcome
  - → Bodyweight -10%
  - → Total body fat -19%
  - → Decreased liver fat

CV benefit not yet studied

- CV risk factors
  - → Waist circumference -8.3%, **less central obesity**
  - → Reduced insulin resistance
  - → Decrease in systolic BP
  - → Decrease in VLDL, triglycerides
  - → Increase in HDL

Eckard A et al. Lancet Diabetes Endocrinol 2024, p523

Most frequently reported side effects

- Nausea, vomiting, dyspepsia
- Diarrea, constipation
- Elevated lipase
- **Cholelithiases, pancreatitis**
- Fatigue

→ Do not use if history of pancreatitis or thyroid cancer

Access to treatment

Access to GLP-1 in Belgium

Only reimbursed for type 2 diabetes if:

HbA1c >7.5%

AND

BMI>30 kg/m²

Tirzepatide available but NOT reimbursed in Belgium

Restrictions due to limited stocks

Aanbevelingen FAGG ter attentie van (ziekenhuis)apothekers en artsen(-specialisten):

1. *Zolang er sprake is van een beperkte beschikbaarheid, moet er voorrang worden gegeven aan de vergunde indicatie van de GLP-1 analogen voor de behandeling van diabetes mellitus type 2. Dat is de behandeling van volwassen patiënten met onvoldoende gereguleerde diabetes mellitus type 2 als toevoeging aan dieet en lichaamsbeweging.*
2. *Daarnaast kunnen GLP-1 analogen ook voorgeschreven worden voor:*
3. *patiënten met overgewicht waarbij er sprake is van een BMI (Body Mass Index) hoger of gelijk aan 35 kg/m²*
4. *patiënten met overgewicht waarbij er sprake is van een BMI of hoger of gelijk aan 30 kg/m² in combinatie met ten minste één gewichtsgerelateerde comorbiditeit.*

Since 14/11/2023

Priority for patients with type 2 diabetes

Otherwise only in case:

- BMI>35 kg/m²
- BMI>30 kg/m² WITH obesity-related comorbidity

First prescription has to be an endocrinologist!

Prizing per month of treatment (november 2024)

- Semaglutide 1 mg SC 1x/week 103, 80 Euro
- Semaglutide 14 mg ORAL 1x/day 100,74 Euro
- *Tirzepatide 5 mg SC 1x/week** *232,80 Euro*

*10 and 15 mg not yet available, price unknown

Source: BCFI

Important remarks

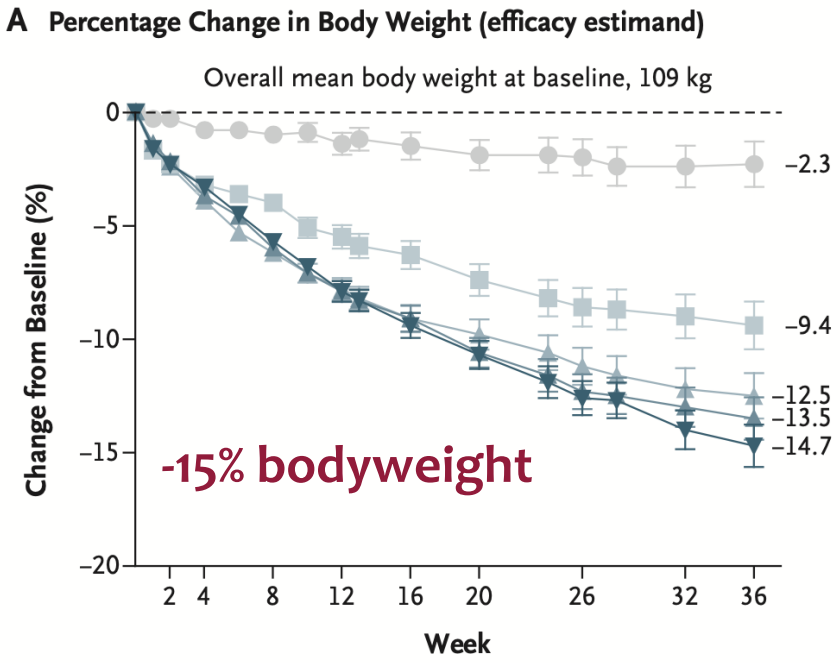
- These drugs do NOT replace nutritional or surgical treatment options
- **Chronic treatment** often needed for maintenance of weight loss
- 66% of lost weight regained within one year of discontinuation (sema 2.4 mg)
- **10-15% non-responders**
- Rebound effect: more fat tissue gained then muscle tissue

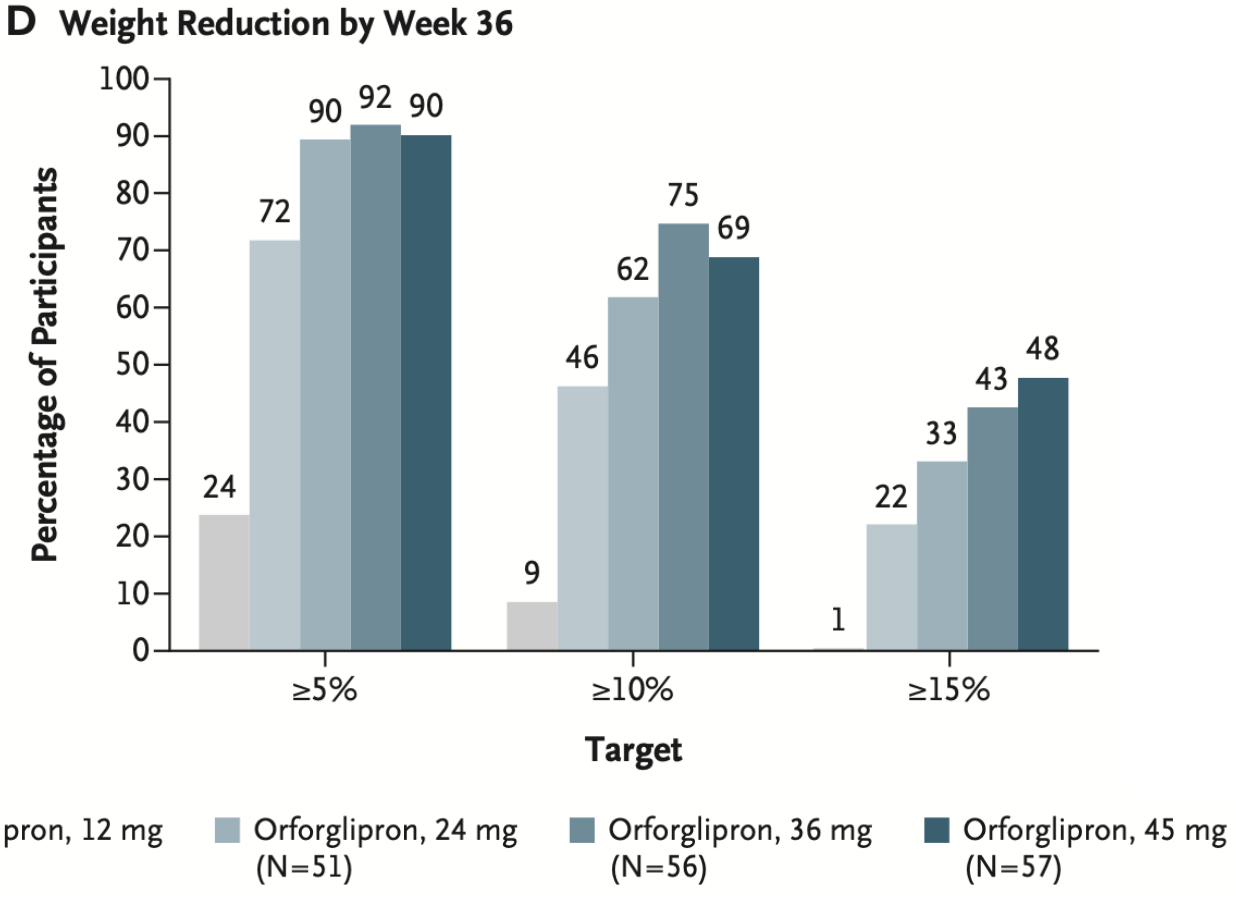
GLP-1 is NO SILVER BULLET!!

Future perspectives

Non-peptide GLP-1 agonist (oral orforglipron) in obesity

Easier production and intake (oral Semaglutide needs fasted intake)





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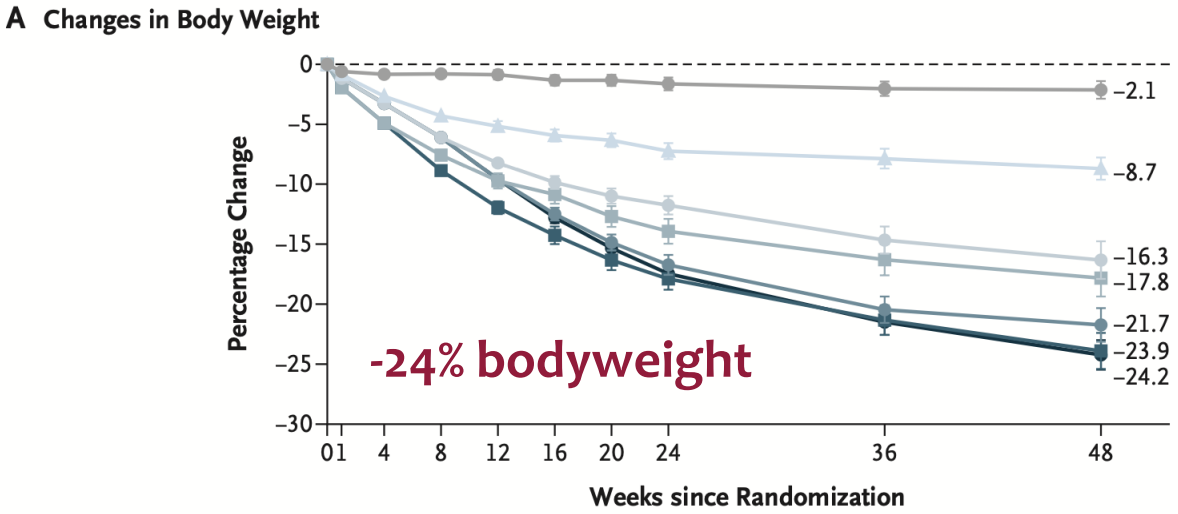
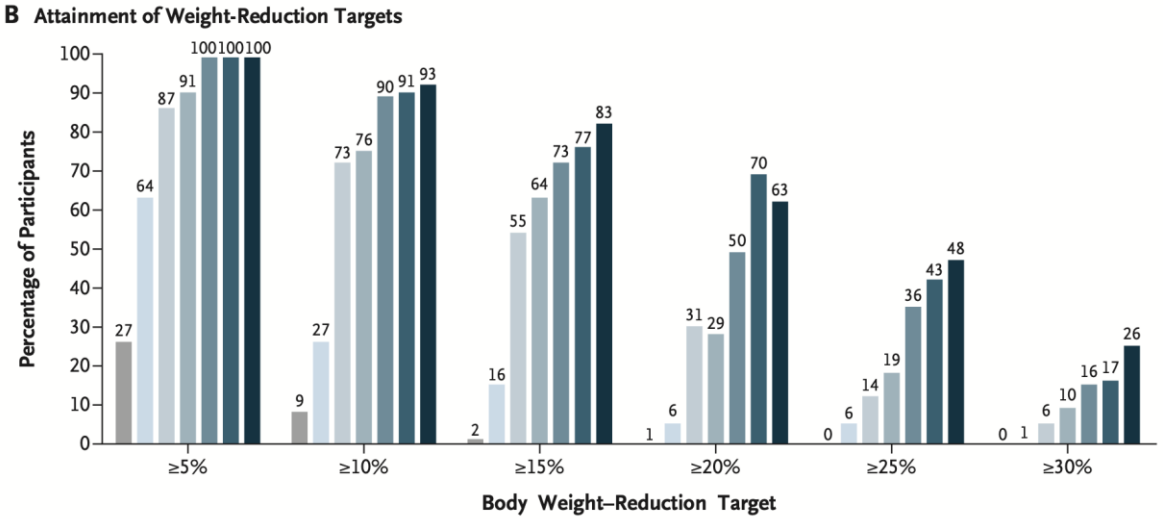
Wharton S et al. NEJM 2023

Tri-agonist (GLP-1, GIP, Glucagon) in obesity





Placebo | Retatrutide, 1 mg | Retatrutide, 4 mg (ID, 2 mg) | Retatrutide, 4 mg (ID, 4 mg) | Retatrutide, 8 mg (ID, 2 mg) | Retatrutide, 8 mg (ID, 4 mg) | Retatrutide, 12 mg (ID, 2 mg)

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Jastreboff A, NEJM 2023

Weightloss in non-diabetic people with obesity

15-24% weight loss in non-diabetics

Weight loss is always more pronounced in non-diabeitc when compared with diabetic people

Doses and drugs NOT yet available in Belgium!

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Conclusion

- **Central obesity** is associated with cardiometabolic syndrome and increased risk for **CV morbidity and mortality**
- Reduction in body fat, especially **visceral abdominal fat**, reduces insulin resistance and CV risk
- **Life-style intervention remains the cornerstone**
- **GLP-1 analogues** reduce bodyweight and CV risk but is **expensive and access is limited**
- GLP-1 analogues have been tested in **PLWHIV** and appear to be **safe and effective** for reduction of central obesity