PainScience

Perioperative Weight Management

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Disclosures

- Pain Specialist
  - Salaried WA Health & Joondalup
  - Director PainScience
- Adjunct Academic Appointments
  - UWA/NDU/Curtin
- Don't accept honorariums, travel or accomodation from industry
  - Do accept education/food/wine
- No financial relationships with anything discussed here

Outline

- Conventional approach to weight management
- Incretin therapies
- Current agents
- Future developments

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Conventional approaches

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Why do this?

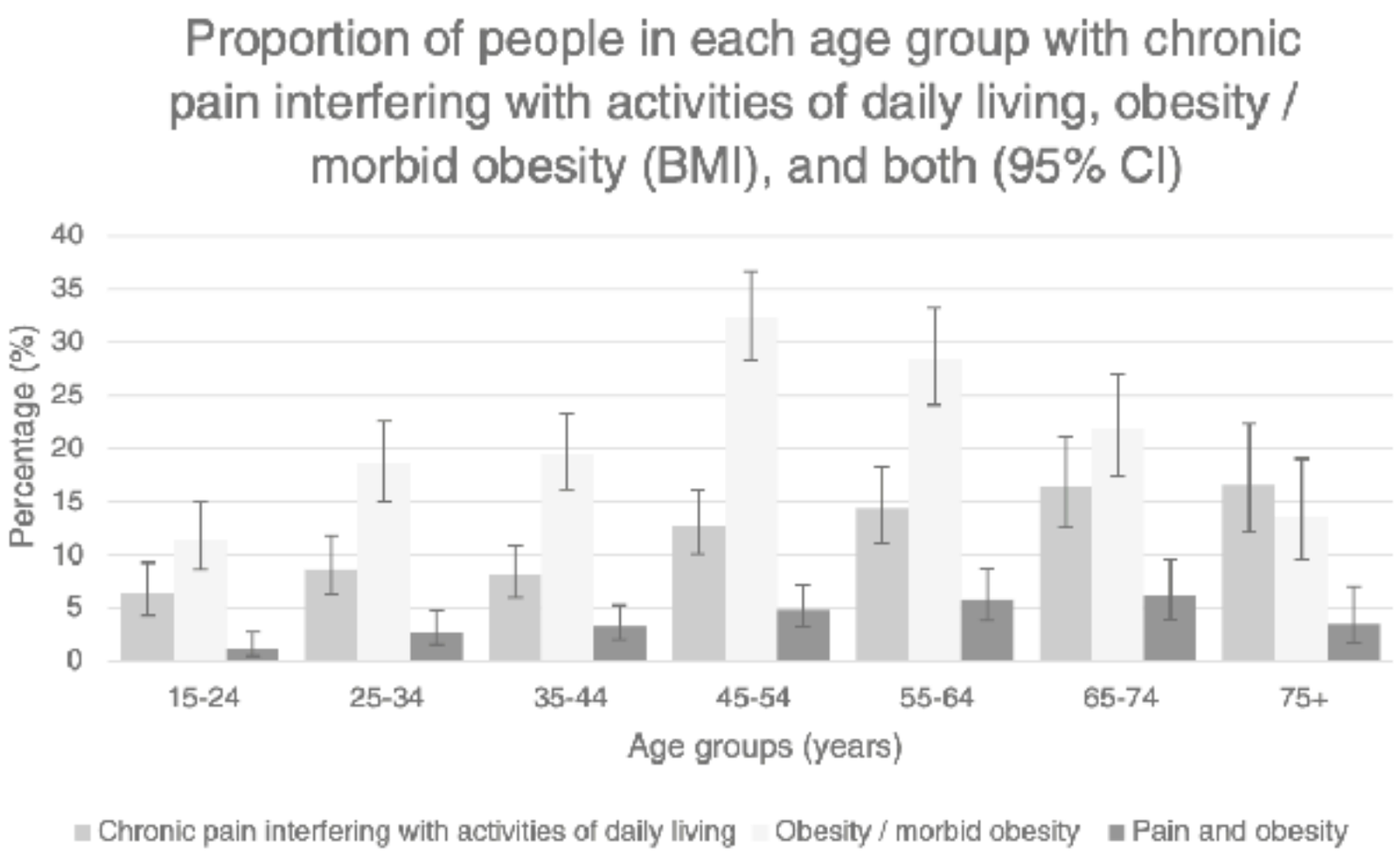

Fig. 1 In 2616 randomly selected community members, proportions with chronic pain interfering with activities of daily living, obesity and both

Allen et al. BMC Public Health (2016) 16:1034 DOI 10.1186/s12889-016-3696-3

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Why do this?

Obesity is treatable

- It is a major contributor to pain issues
- It tends to get ignored

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Weight Regulation

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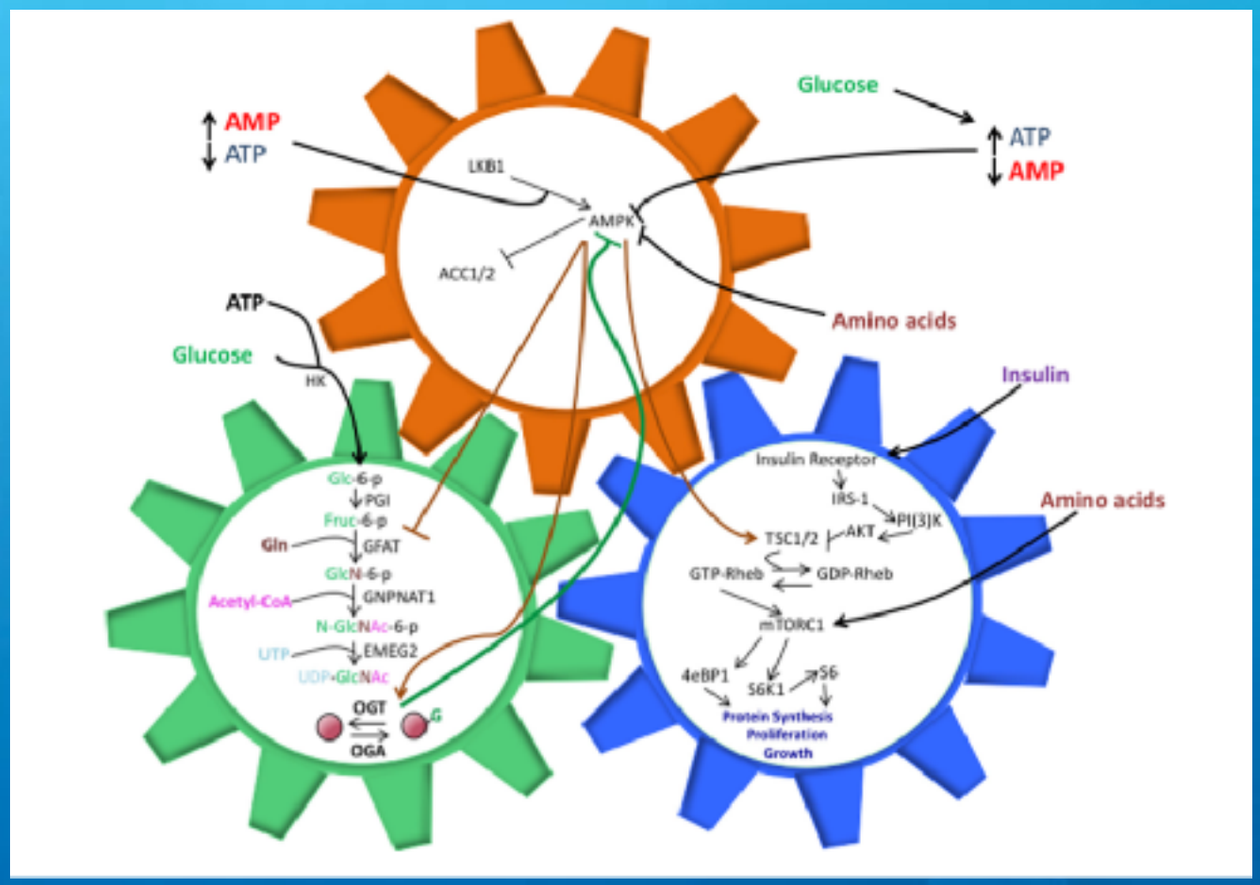
Metabolism

Energy sensing is done at a cellular level

Hexosamine biosynthetic pathway uses 3-5% of cellular glucose

mTOR -> cell proliferation (C1) cell survival (C2). Activated by amino acids and insulin.

AMPK -> inverse response to ATP levels



Cork GK, Thompson J and Slawson C (2018) Real Talk: The Inter-play Between the mTOR, AMPK, and Hexosamine Biosynthetic Pathways in Cell Signaling. Front. Endocrinol. 9:522. doi: 10.3389/fendo.2018.00522

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Energy sensing mechanisms

Low energy - AMPK activates.

- Cellular function slows down

High energy mTOR activates

- Cells grow and divide. (Normal and cancer cells)
- Inflammatory effects

This is seen in every cell in every complex (multicellular) organism.

What about higher functions?

Hypothalamic AMPK is a major mediator of energy balance.

Activation leads to:

- Induced appetite

- Decreasing thermogenesis and basal metabolic rate

Hypothalamic neurons in the arcuate nucleus release

Neuropeptide Y (hunger)
Pro-opiomelanocortin (saiety)

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Decreasing Hypothalamic AMPK

GLP-1

Produced by neurons in nucleus solitary tract. suppresses appetite.

Inhibits AMPK activation with fasting

Insulin

Central administration of insulin produces satiety.

Insulin resistance in the brain leads to hyperphagia.

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Conventional Diet and Exercise

Its just math, right?

Is body weight controlled by the combination of:

Body weight change = Total calorific intake - Energy expenditure

To lose 1Kg of body fat you need a deficit of

Around 7700 calories (Approx 32000-40000 kilojoules)

So over 40 years, to stop a 40 Kg weigh gain (1Kg/year)

Reduce calories by 21per day.

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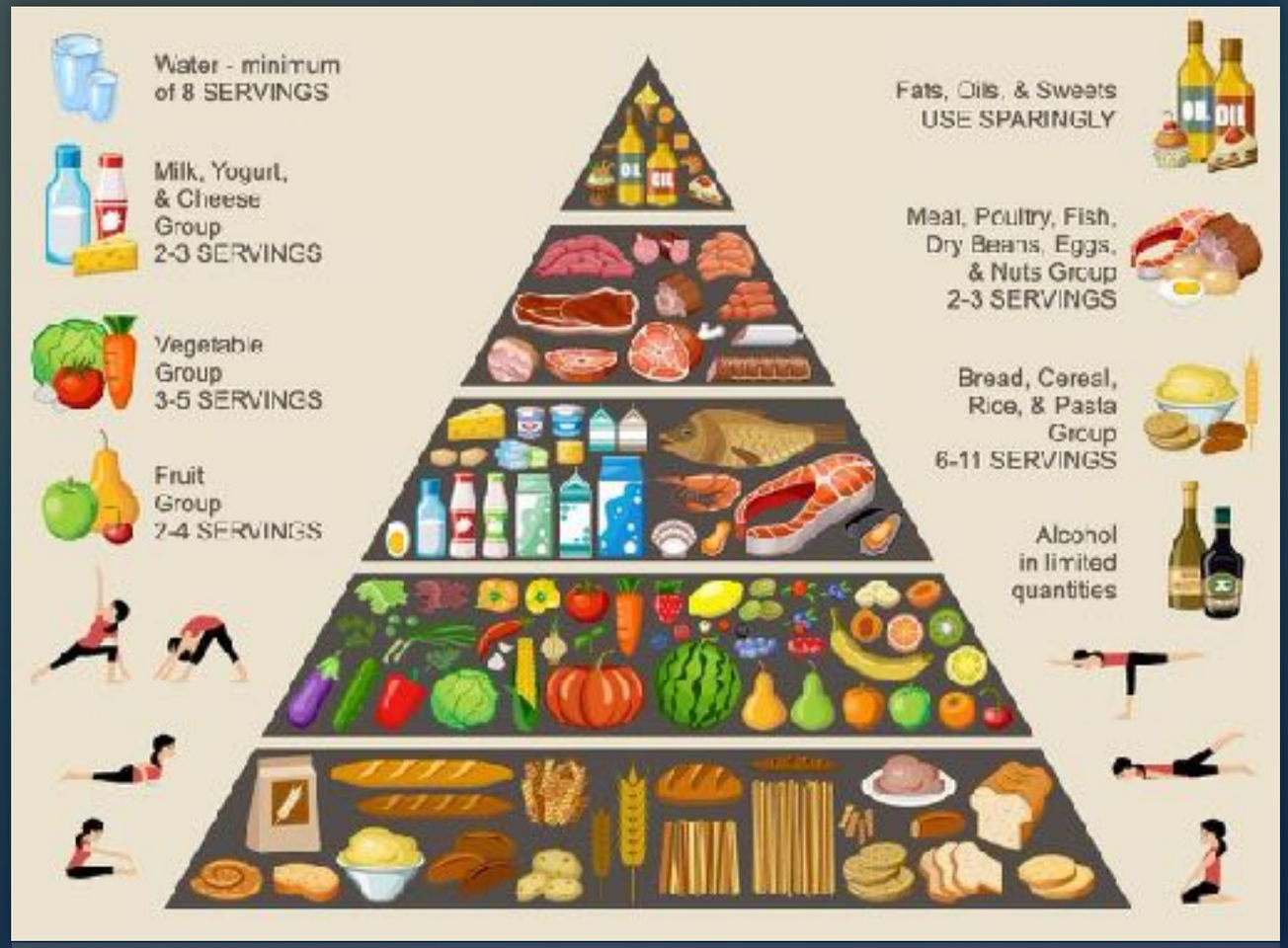
Diet - What you eat.

Lots and lots of diets out there.

- Calorie restriction
  - Built on the idea that all calories are equal.
- Healthy Eating Diets
  - Food pyramid
- Low carbohydrate diets
  - Mediterranean / Keto / Atkins / Low GI index


Water - minimum of 8 SERVINGS
Milk, Yogurt, & Cheese Group 2-3 SERVINGS
Vegetable Group 3-5 SERVINGS
Fruit Group 2-4 SERVINGS
Fats, Oils, & Sweets USE SPARINGLY
Meat, Poultry, Fish, Dry Beans, Eggs, & Nuts Group 2-3 SERVINGS
Bread, Cereal, Rice, & Pasta Group 6-11 SERVINGS
Alcohol in limited quantities

Diet

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Food pyramid

Swedish origin in 1970's

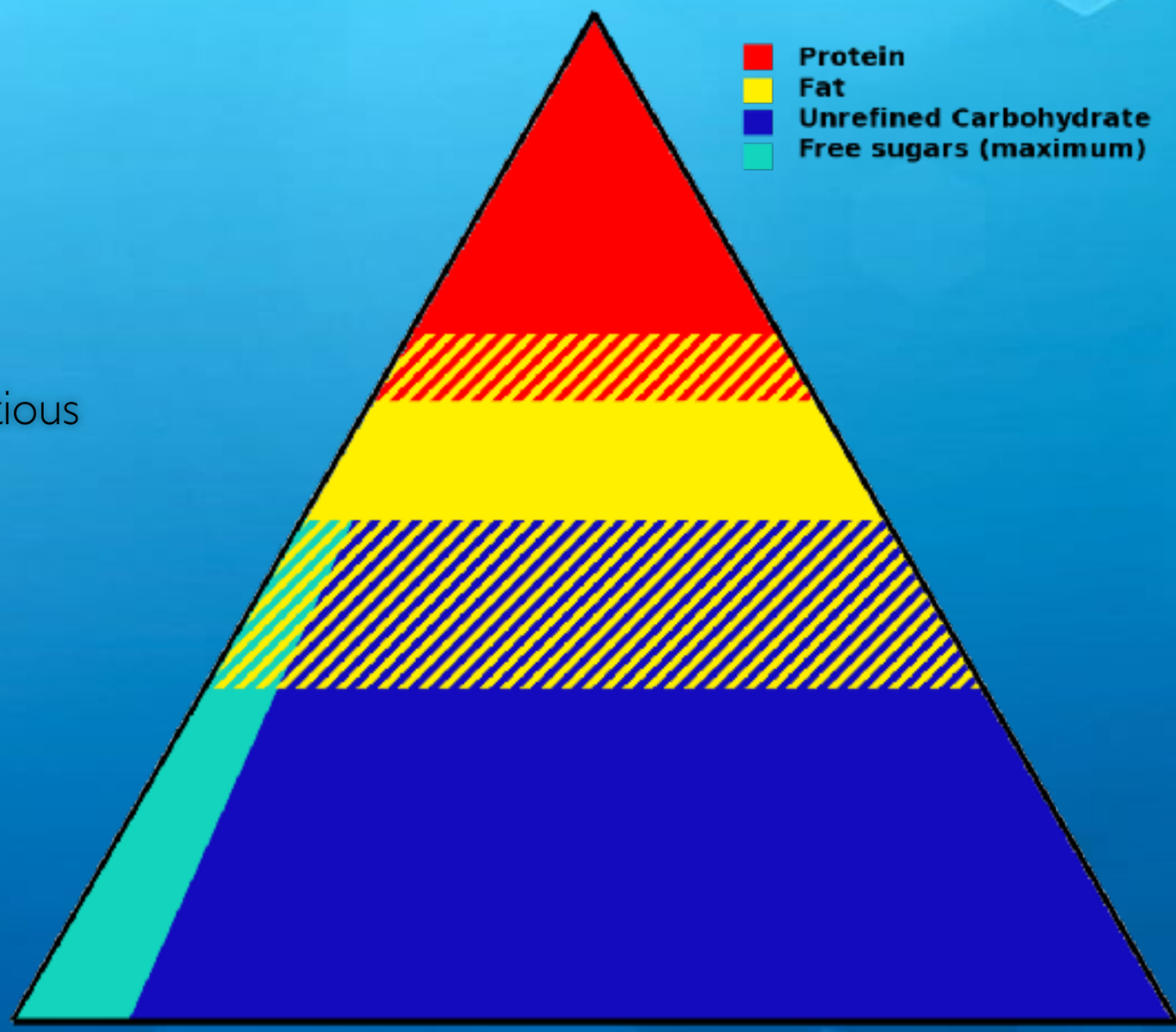
Driven by high food prices

Basic foods that were cheap

Supplemental foods that were nutritious

Adopted worldwide

Heavily modified by industry



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Diet - When you eat

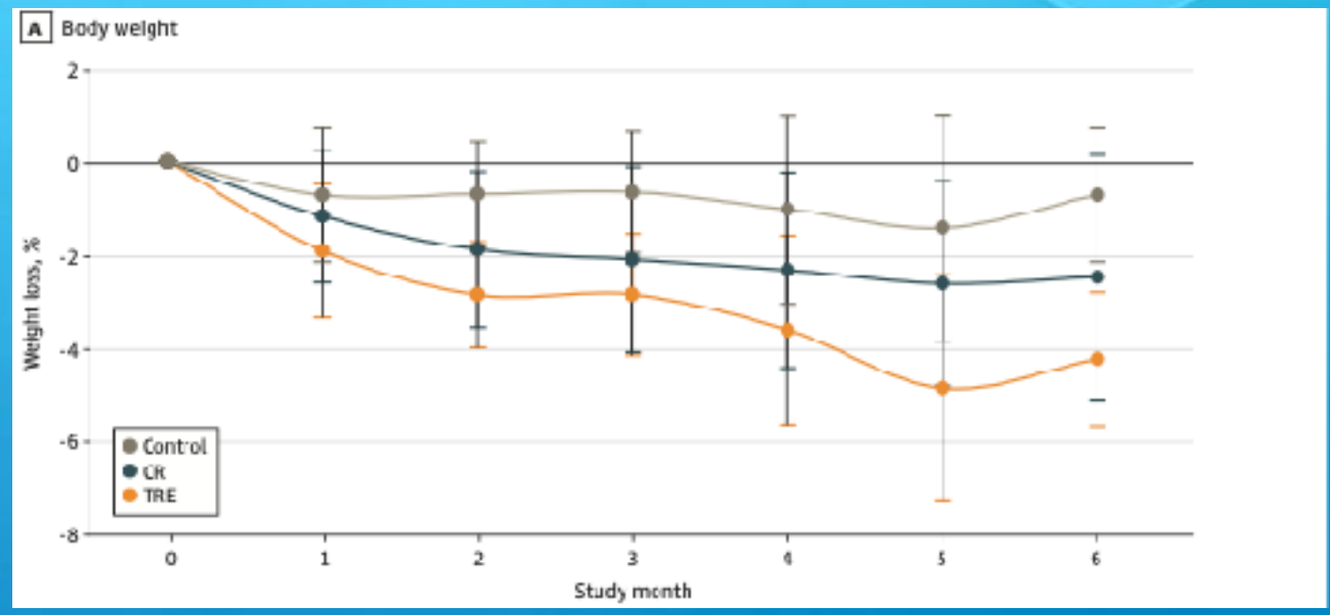
Time restricted feeding &
Intermittent fasting

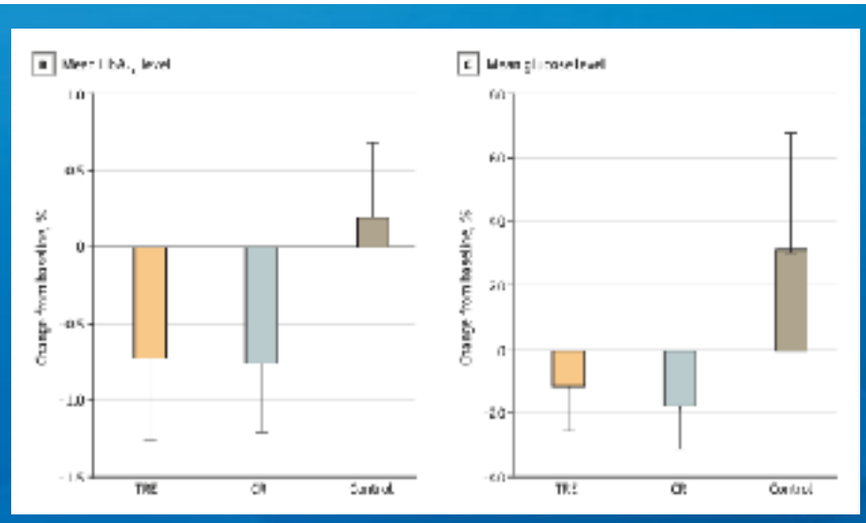
3-4 Days fasting per month

5:2 fasting (calorie restricted days)

16:8 time restricted feeding

Probably best to not eat in the evening.





JAMA Network Open. 2023;6(10):e2339337. doi:10.1001/jamanetworkopen.2023.39337

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Exercise

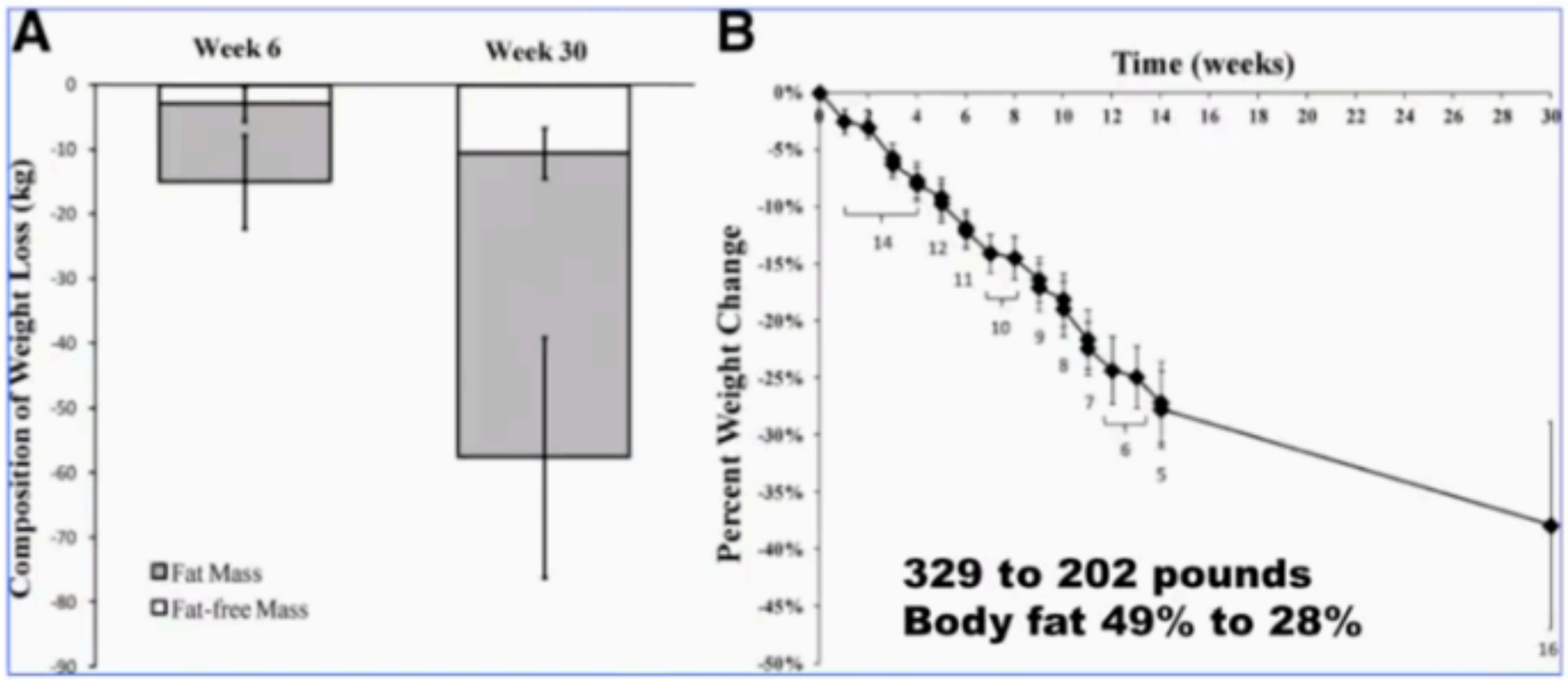
Exercise alone probably doesn't work.

- Its good for you in lots of other ways

So what if you add in exercise plus diet?

THE BIGGEST LOSER
EAT LESS, MOVE MORE

The Biggest Loser Diet



J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

Evidence for Diet

Real world diet programs usually get about six months:

Eat less, move more.

The Biggest Loser Diet

- Reduce Calories
- Increase Exercise

- Eat Less, Move More
- 2015 Rankings
  - #3 Weight Loss
  - #11 Overall

BEST DIETS
U.S.News & WORLD REPORT
RANKINGS

The Biggest Loser

"NBC never does a reunion. Why? We're all fat again"

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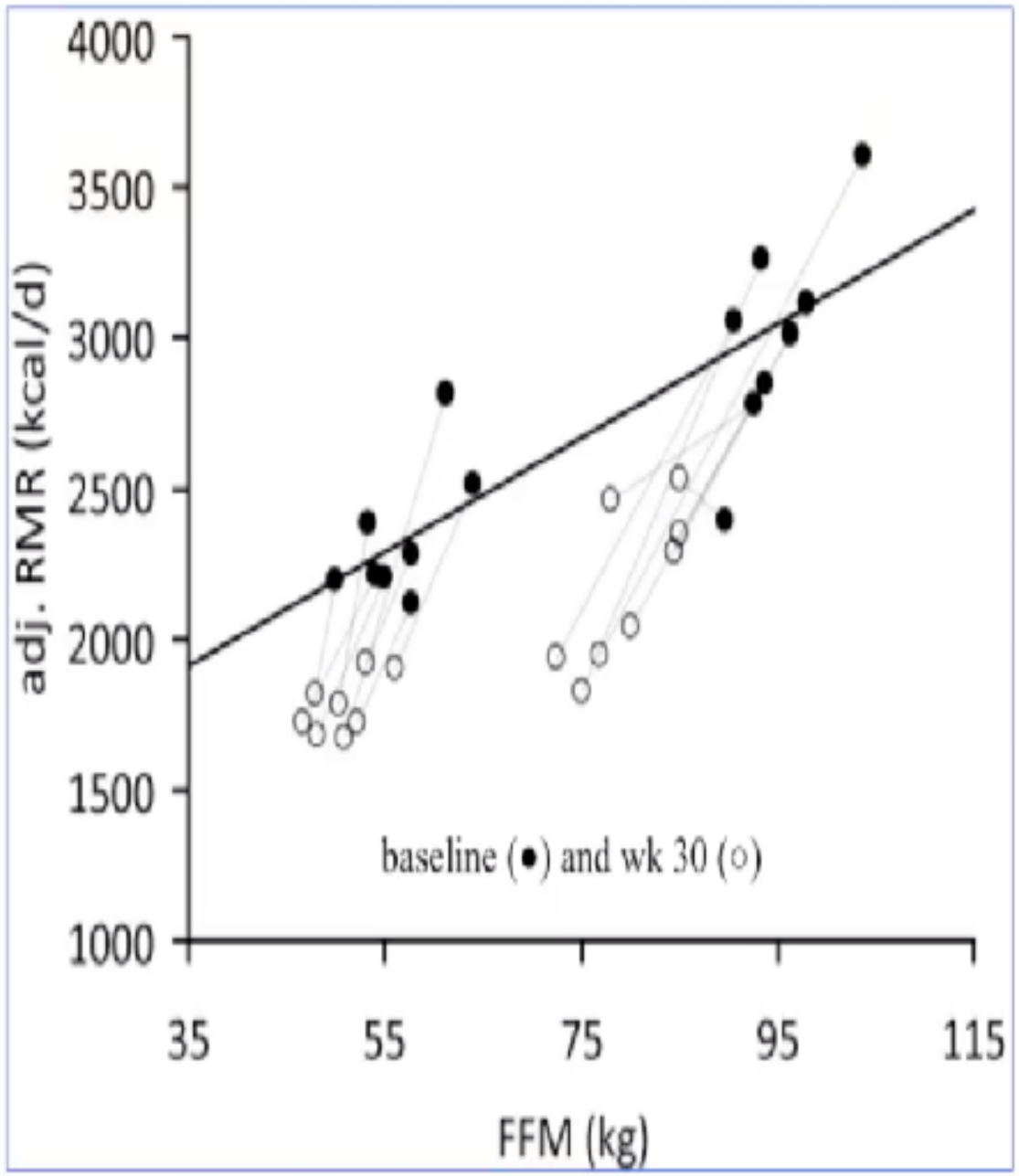
Metabolism slows down

Every single person who entered the biggest loser slowed their metabolism

Average was 700 cal/day reduction.

Everyone feels awful.

Decreased Metabolism



J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

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Exercise
2013 Guideline for obesity Mx

Exercise with reduced calorie diet and behaviour therapy.*

Short term weight loss of 8 kg (5-10% total body weight)

Long term weight gain of 1-2 Kg/year after first year.

High intensity exercise / medically supervised very low calorie *

14 to 21kg loss over 11-14 weeks, weight regain 3 to 4 Kg over 6 months

Low to moderate intensity lifestyle interventions have not been shown to be effective *

* High level of evidence

Circulation. 2014 June 24; 129(25 Suppl 2): S102–S138.
doi:10.1161/01.cir.0000437739.71477.ee.

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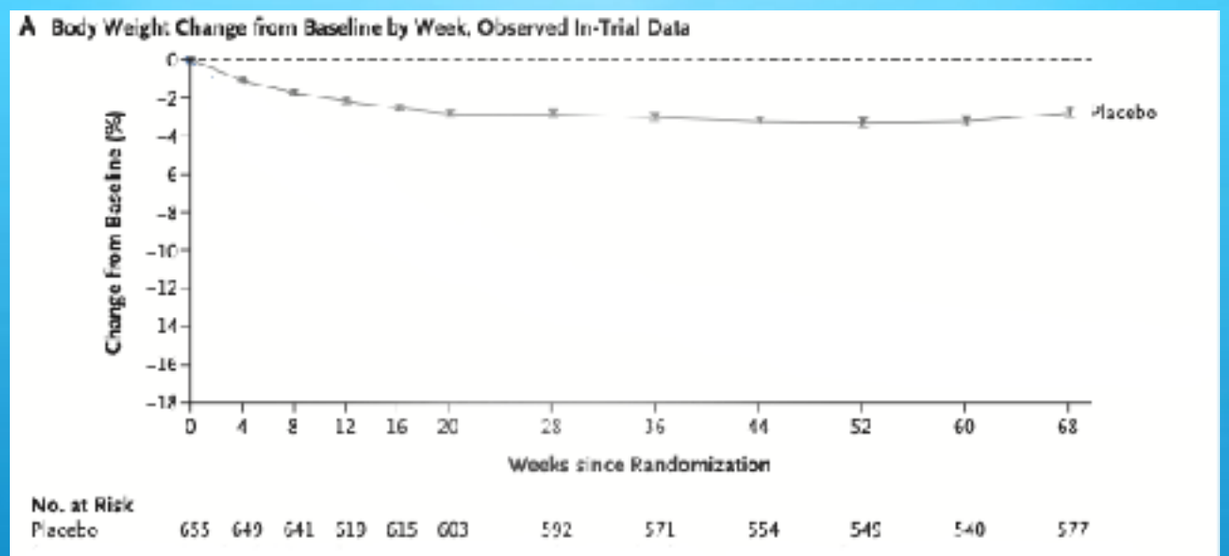
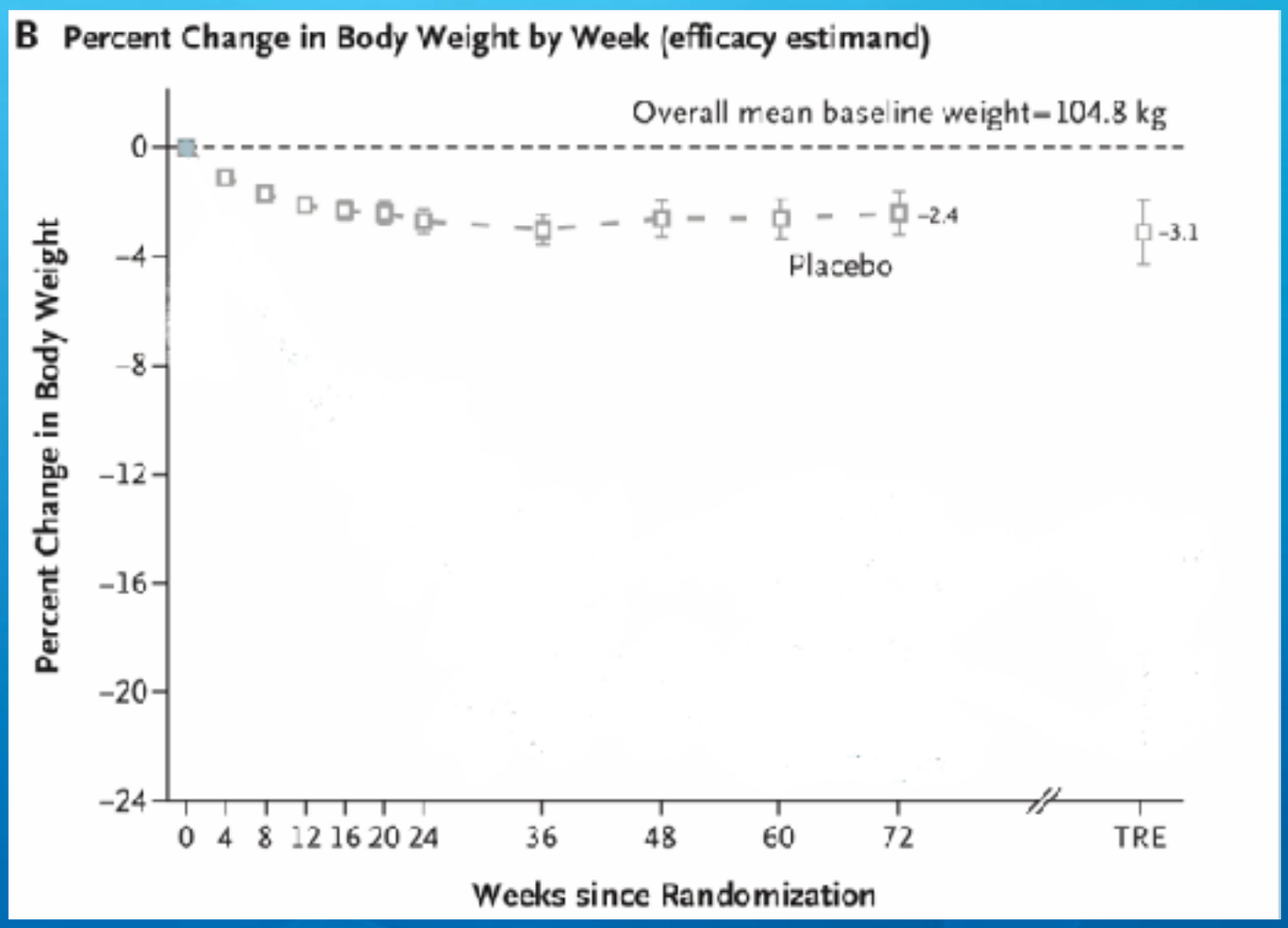
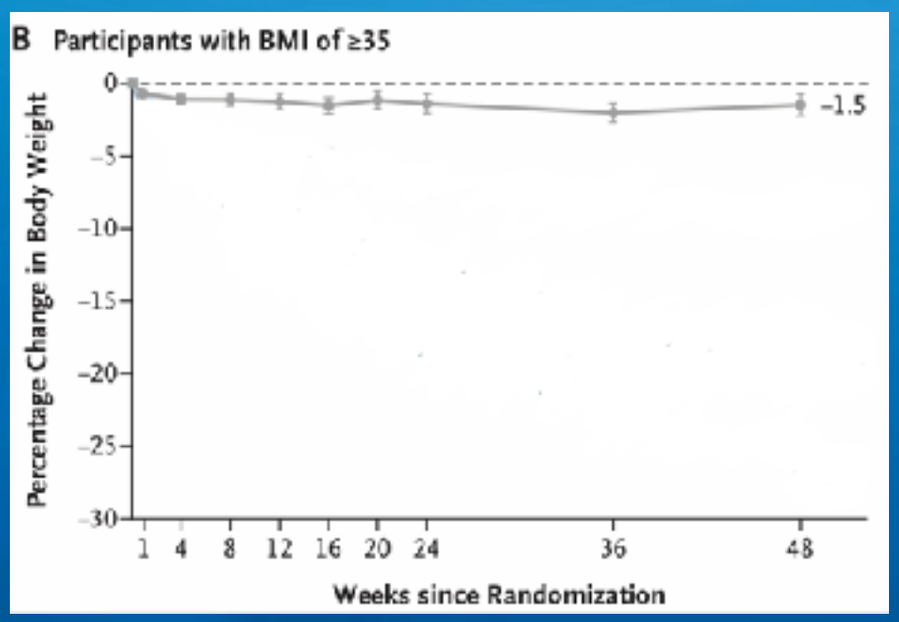
Outcome Data







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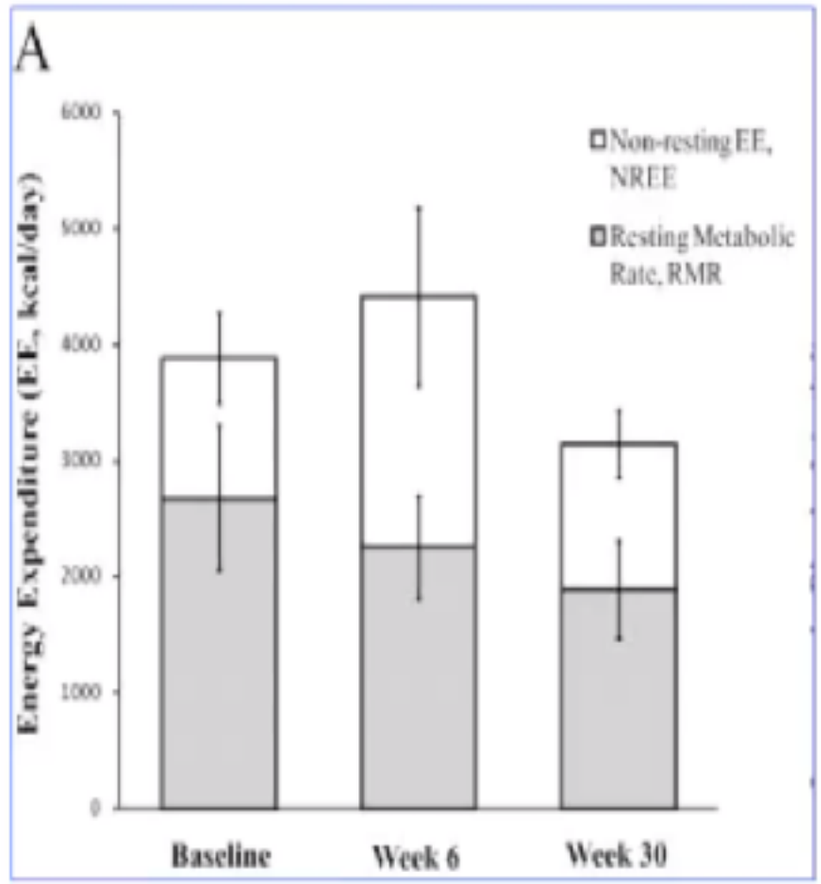
So how do we manage obesity?

We tell everyone to eat less and exercise more

We know that the evidence base is that this will fail

Then we blame the patient for failing a treatment we have prescribed that lacked evidence for long term efficacy.

Decreased Metabolism



J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

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SURGERY

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Bariatric Surgery

Very effective in controlling T2DM

Published data

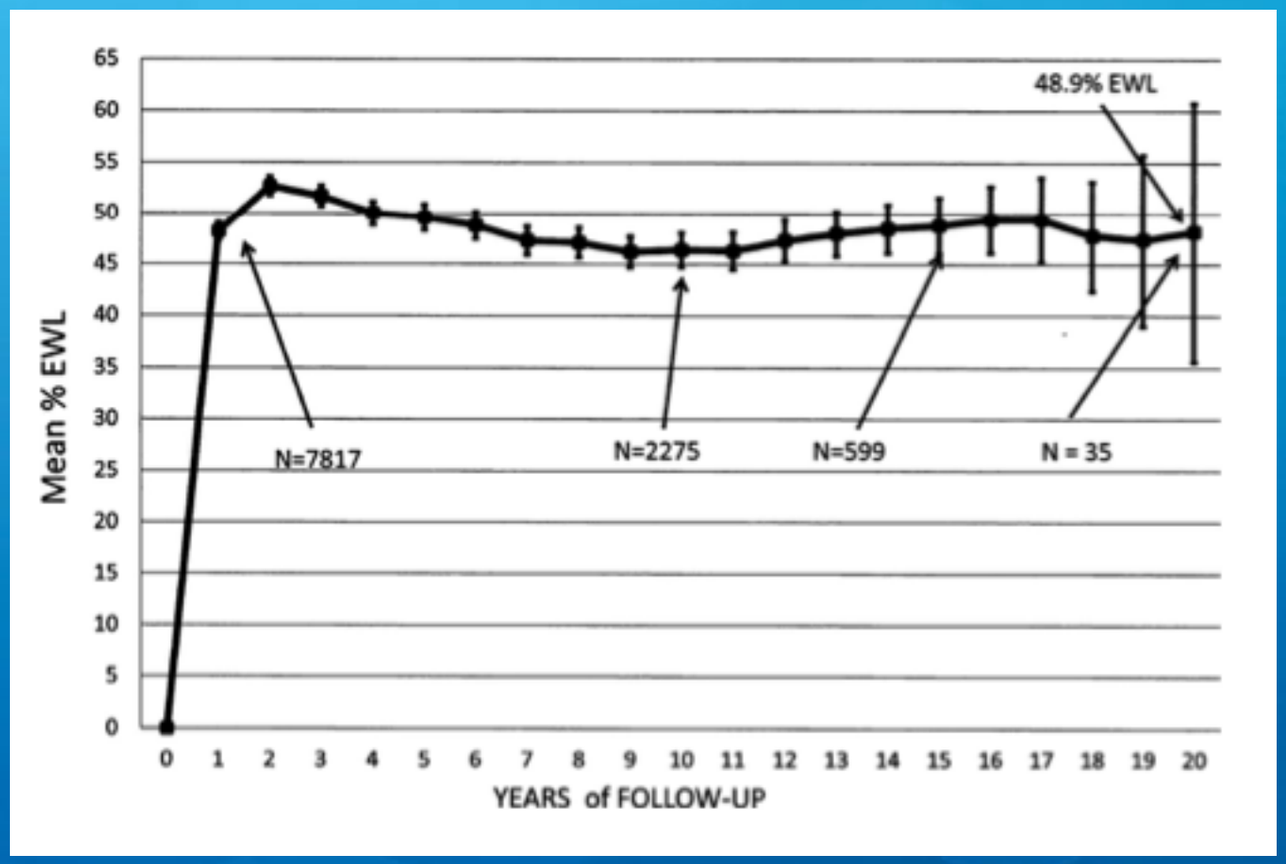
Gastric Bypass 56.7% TBW

Gastric Banding 45.9%

Sleeve Gastrectomy 58.3%

Diabetic control occurs before significant weight loss

Gastric Band Long Term Results



Obesity Surgery (2019) 29:3–14 https://doi.org/10.1007/s11695-018-3525-0

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LESS COMMON & OLDER AGENTS

Medications

Phentermine (Duromine) - similar to amphetamine

- releases dopamine, typically 5-10% body weight loss

Significant side effects

hypertension, tachycardia

rarely stroke, angina, cardiac failure

pulmonary hypertension, cardiac valve disease

CNS overstimulation

GI effects - Nausea and vomiting

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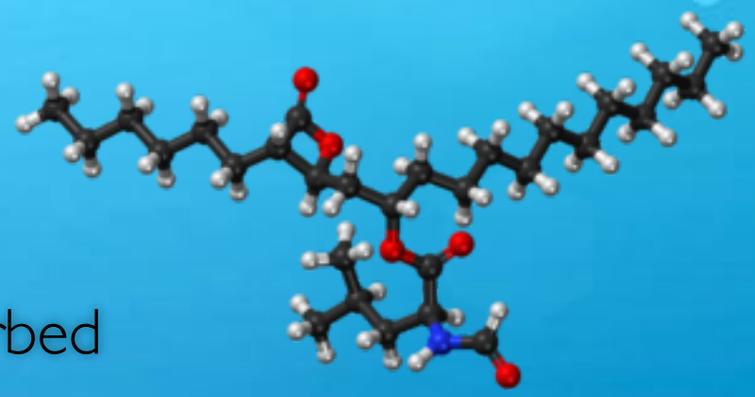
Orlistat

Inhibits gastric and pancreatic lipase

- Prevents breakdown of triglycerides in intestine
- Prevents about 30% of dietary fat from being absorbed



Poorly absorbed - mostly GI side effects

- Steatorrhoea (common) Renal injury (rare) Liver injury (very rare?)

Small weight loss (3-4%)

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SGLT-2 Inhibitors

Introduced for T2DM (loss of 50-100g urinary glucose)

- Very effective diuretics.
  - Can improve diastolic failure
  - Protect against renal disease progression

Small weight loss effect (1-3 Kg in most studies)

Side effects due to local irritation/infection

Major issues with fasting and surgery
(Euglycaemic ketosis)

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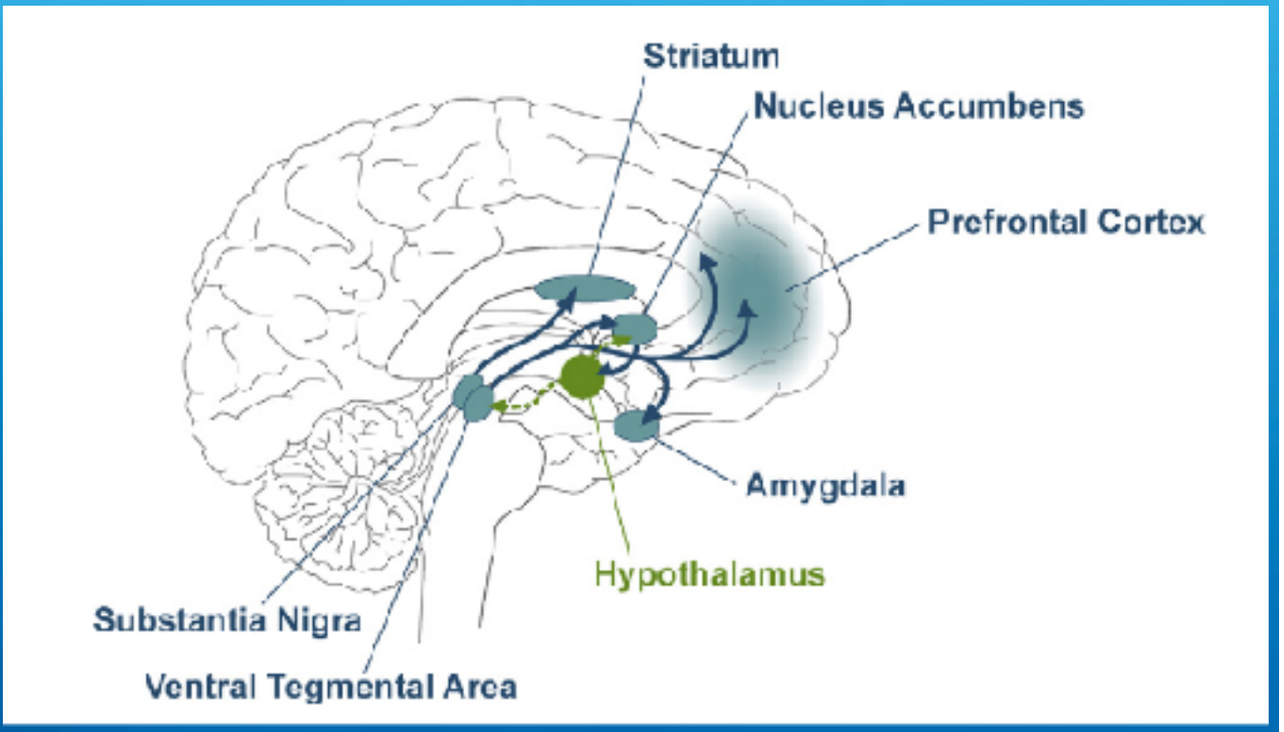
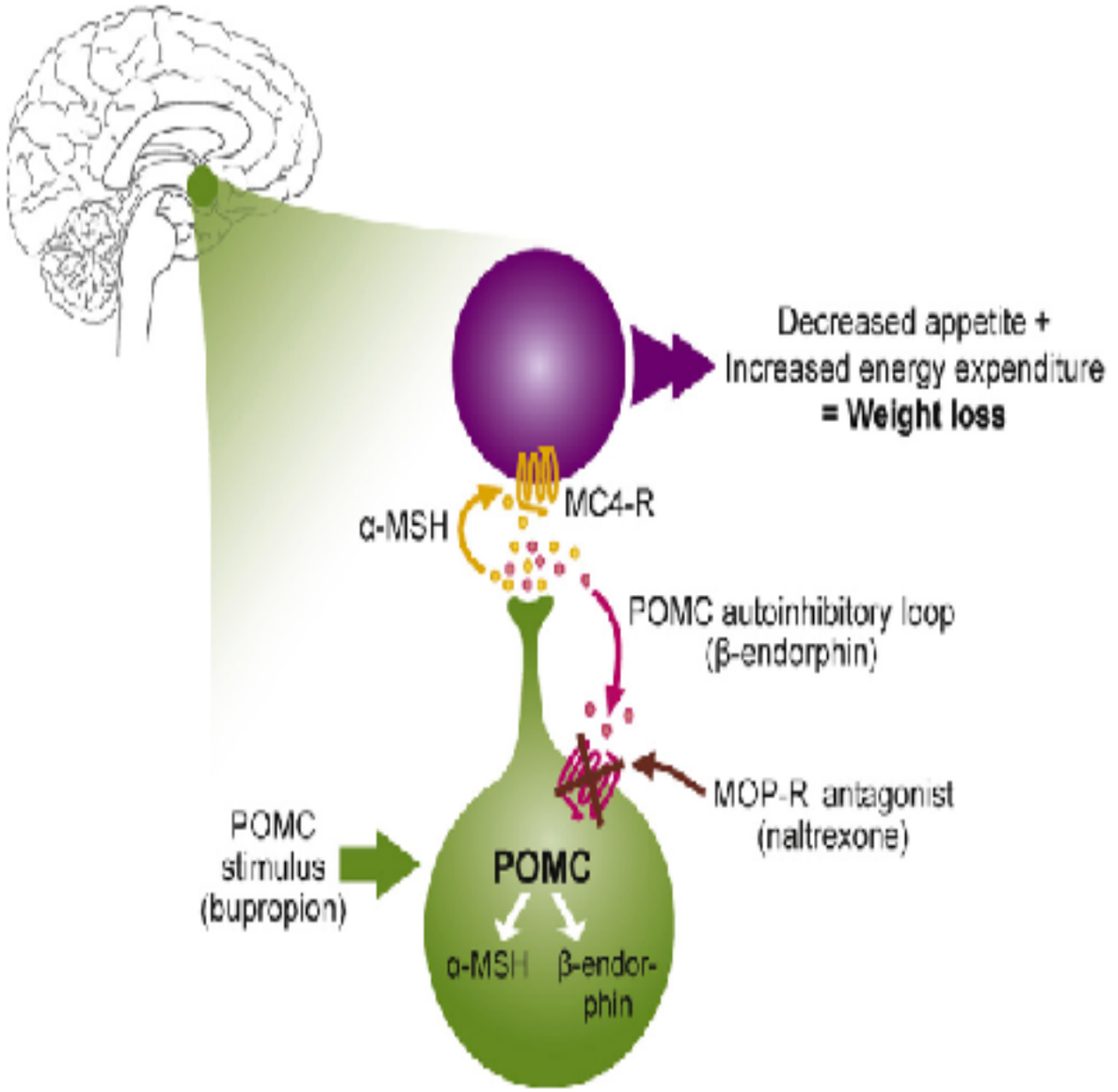
Hypothalamic Weight Regulation

Based on research that looked at central regulation of satiety





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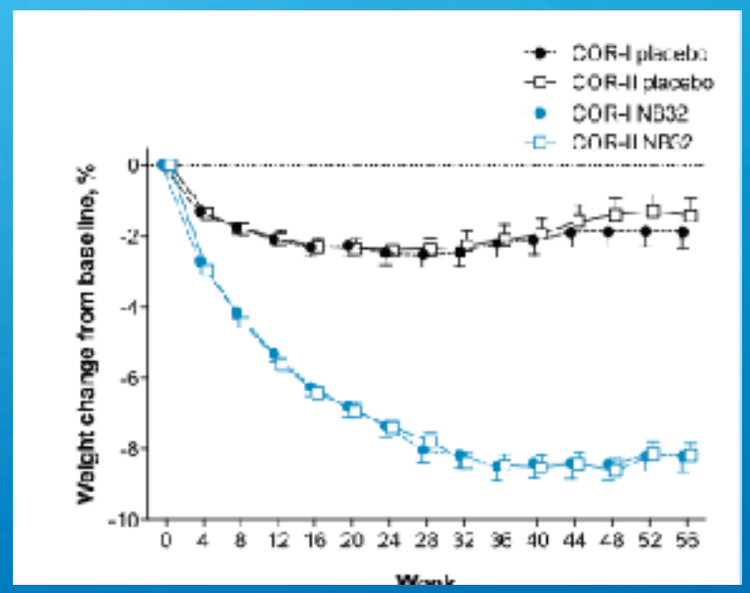
Bupropion/Naltrexone

Naltrexone 8mg/Bupropion 90mg (ii BD). (32/360mg daily)

Half of patients lose >5% TBW (Half don't)

Most studies show 5-8% TBW loss

Quarter of patients lose >10% TBW



Significant side effect profile

Nausea/Constipateion/Headache/Vomiting

Possible issues with blood pressure, heart rate and seizures

Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss. Sonja K. Billesa, Puspha Sinnayahb, Michael A. Cowley
http://dx.doi.org/10.1016/j.phrs.2014.04.004

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Incretin therapy

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GLP-1 Receptor Agonists

Many available:

Exenatide / Dulaglutide / Liraglutide / Semaglutide

(Also Lixisenatide, albiglutide, efpeglenatide)

Mimic Glucagon Like Peptide to produce:

Reduction in glucagon and hepatic gluconeogenesis

Reduction in appetite and gastric emptying, reduced calorie intake.

Improved diabetic control

Reduced HbA1C & preserved hypoglycaemic responses

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INCRETIN SAFETY

Side effects are common but safety is high.

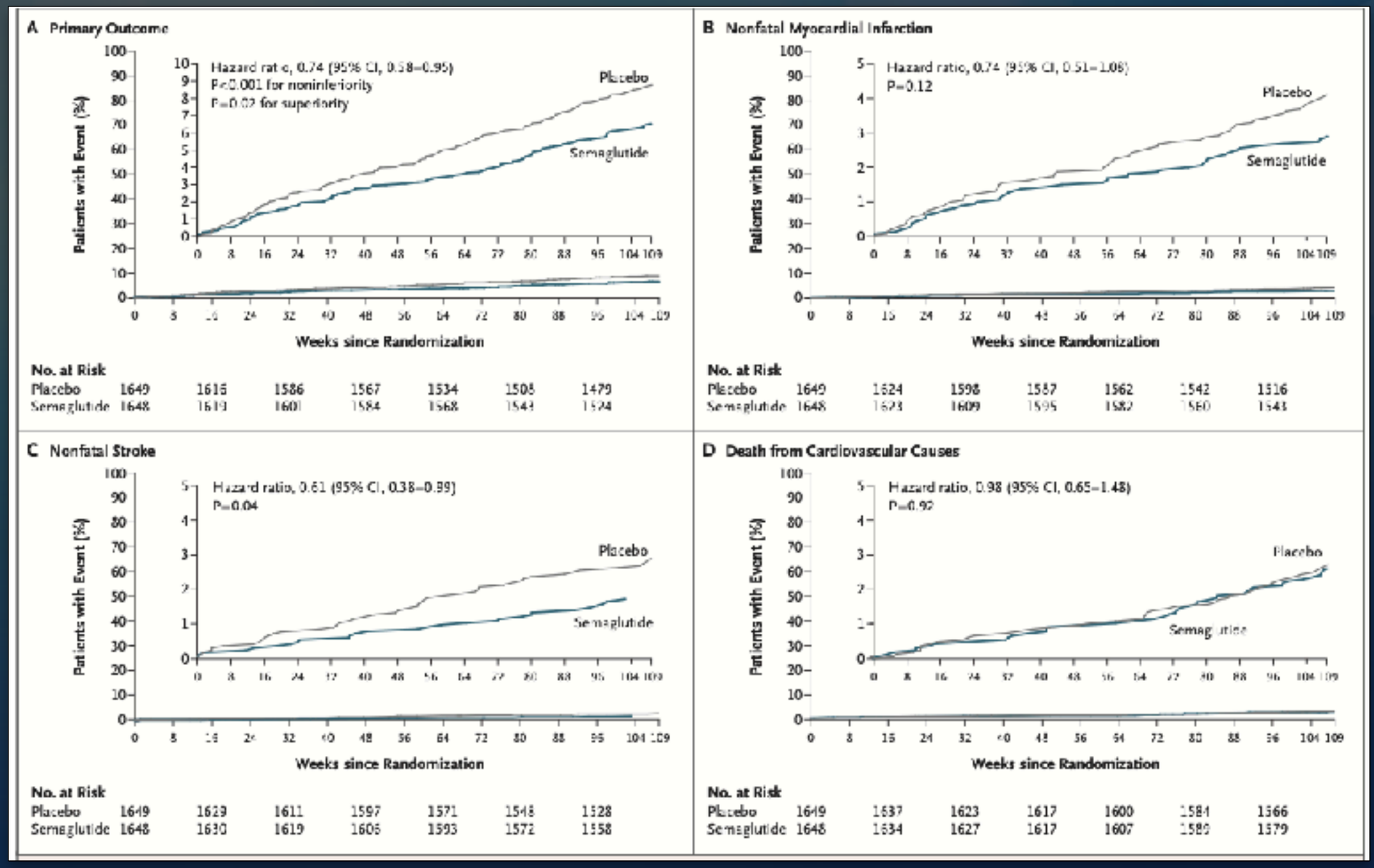
Many side effects shared with placebo

GI side effects are more common

Severe adverse reactions are probably overstated

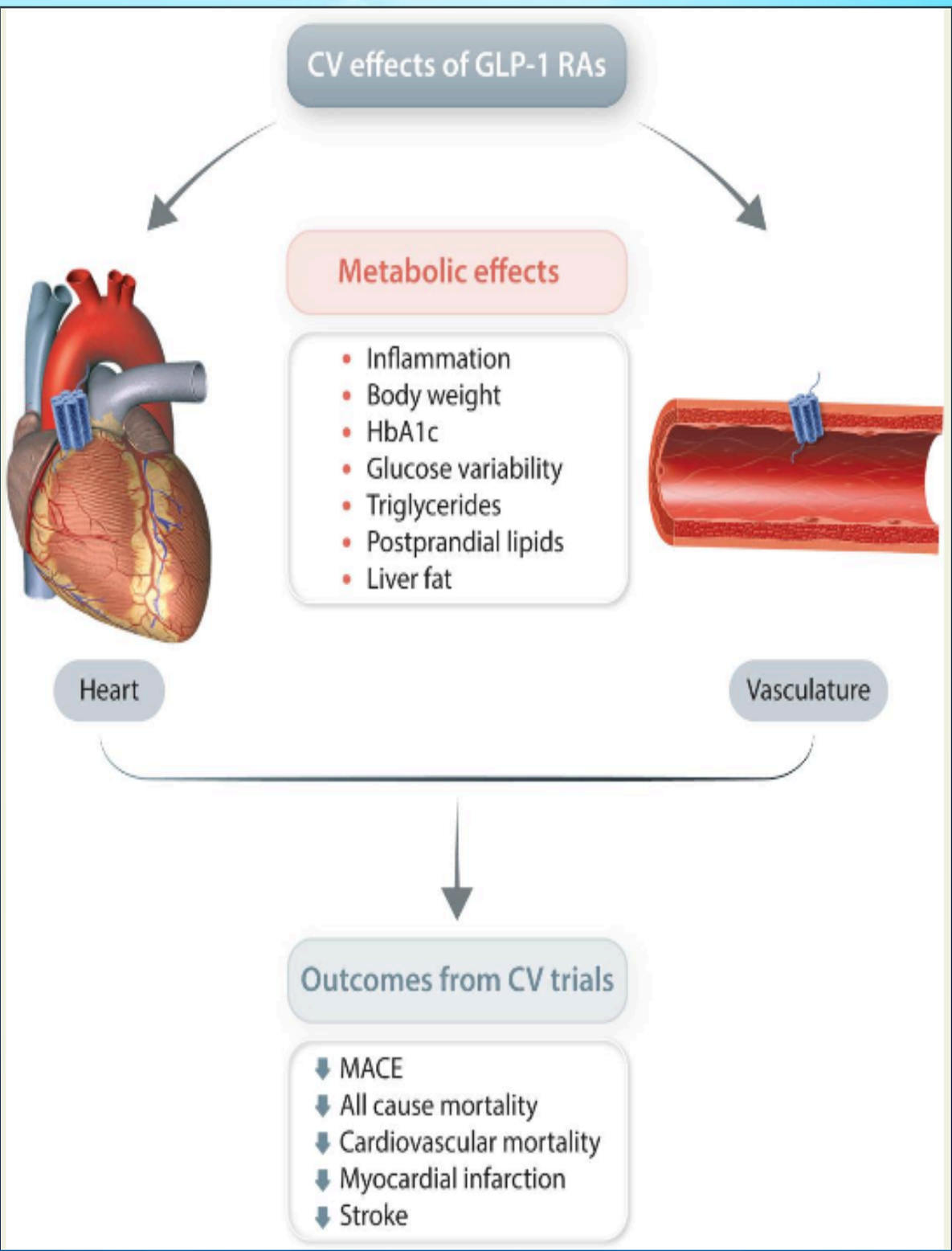
N ENGL J MED 2016;375:1834-44.
DOI: 10.1056/NEJMOA1607141

Event	Semaglutide		Placebo	
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)
	number of patients (percent)			
Adverse event	740 (89.6)	732 (89.1)	748 (90.8)	736 (89.2)
Serious adverse event†	289 (35.0)	276 (33.6)	329 (39.9)	298 (36.1)
Severe adverse event‡	200 (24.2)	207 (25.2)	216 (26.2)	194 (23.5)
Adverse event leading to treatment discontinuation	95 (11.5)	119 (14.5)	47 (5.7)	63 (7.6)
Nausea	18 (2.2)	38 (4.6)	2 (0.2)	2 (0.2)
Vomiting	14 (1.7)	23 (2.8)	3 (0.4)	2 (0.2)
Diarrhea	15 (1.8)	19 (2.3)	5 (0.6)	2 (0.2)
Gastrointestinal disorder§	419 (50.7)	430 (52.3)	294 (35.7)	290 (35.2)
Diarrhea	148 (17.9)	151 (18.4)	98 (11.9)	87 (10.5)
Nausea	143 (17.3)	180 (21.9)	62 (7.5)	67 (8.1)
Vomiting	87 (10.5)	122 (14.8)	43 (5.2)	34 (4.1)
Cardiac disorder§	173 (20.9)	150 (18.2)	189 (22.9)	173 (21.0)
Atrial fibrillation	27 (3.3)	23 (2.8)	32 (3.9)	26 (3.2)
Acute pancreatitis¶	6 (0.7)	3 (0.4)	3 (0.4)	9 (1.1)
Gallbladder disorder‖	32 (3.9)	26 (3.2)	38 (4.6)	23 (2.8)
Cholelithiasis	21 (2.5)	17 (2.1)	19 (2.3)	12 (1.5)
Acute cholecystitis	4 (0.5)	0	6 (0.7)	2 (0.2)
Severe or symptomatic hypoglycemic event**	191 (23.1)	178 (21.7)	177 (21.5)	173 (21.0)
Acute renal failure‖	42 (5.1)	23 (2.8)	34 (4.1)	35 (4.2)
Allergic reaction‖	49 (5.9)	49 (6.0)	46 (5.6)	57 (6.9)
Injection-site reaction‖	8 (1.0)	9 (1.1)	9 (1.1)	12 (1.5)
Neoplasm¶	66 (8.0)	89 (10.8)	70 (8.5)	69 (8.4)
Benign	40 (4.8)	54 (6.6)	36 (4.4)	34 (4.1)
Premalignant	4 (0.5)	6 (0.7)	3 (0.4)	2 (0.2)
Malignant				
Any	26 (3.1)	40 (4.9)	35 (4.2)	35 (4.2)
Pancreatic	0	1 (0.1)	2 (0.2)	2 (0.2)



Semaglutide Outcomes

N Engl J Med 2016;375:1834-44. DOI: 10.1056/NEJMoa1607141



Cardiac Incretin Effects

Decreased cardiovascular risks

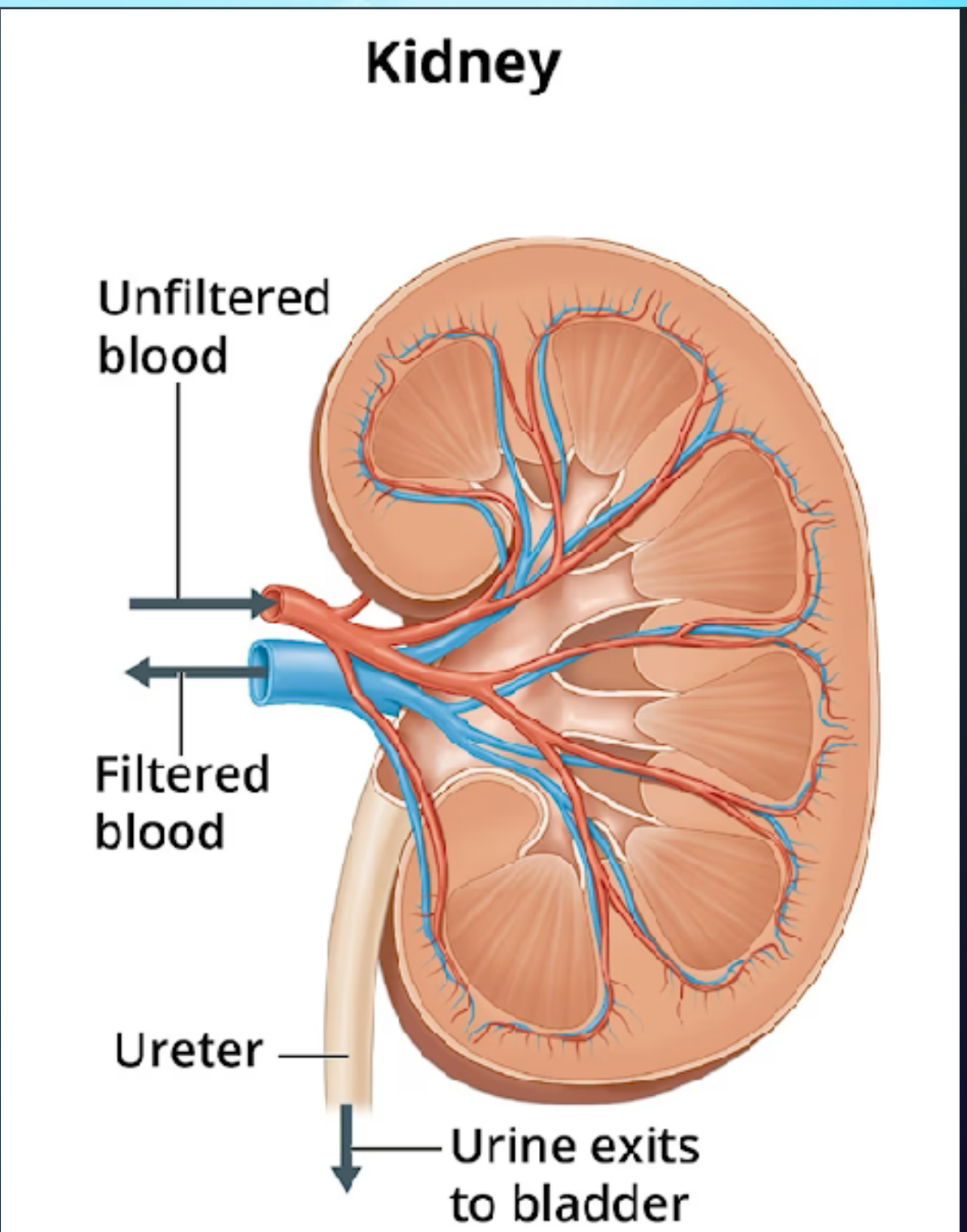
Benefits probably not just due to improvement in glycemic control, but includes this.

- Small decrease in systolic BP (↓ 3 mmHg)
- Reduced inflammatory markers (TNF/IL1,6)
- Reduced macrophage activation
- Reduced hospital admissions

Conventional therapy

Insulin/Sulphonylureas ↑ cardiac risk & mortality

Cardiovascular Research (2023) 119, 886–904
https://doi.org/10.1093/cvr/cvac112



Other Effects

Renal Effects In type 2 diabetes

Reduction of macroalbuminuria

Potential slowing of early diabetic renal disease

Most evidence is for slowing early onset of renal disease. Benefit in late disease is limited.

Retinopathy

May worsen if already present.

Cardiovascular Research (2023) 119, 886–904
https://doi.org/10.1093/cvr/cvac112

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Cardiovascular outcomes

Table 2 Summarizes the key results from eight CVOT trials

GLP-1 RA	Trial	N	Follow-up (years)	Baseline HbA1c (%)	MACE HR (95% CI)	CVD mortalitet HR (95% CI)	Fatal or non-fatal myocardial infarction HR (95% CI)	Fatal or non-fatal stroke HR (95% CI)	All-cause mortality HR (95% CI)
Lixisenatide	**ELIXA** (Reference[69])	6068	2.1	7.7%	1.02(0.89–1.17) P = 0.776	0.98(0.78–1.22) P = 0.85	1.03(0.87–1.22) P = 0.71	1.12(0.79–1.58) P = 0.54	0.94(0.78–1.13) P = 0.50
Liraglutide	**LEADER** (reference[57])	9340	3.8	8.7%	**0.87(0.78–0.97) P = 0.015**	**0.78(0.66–0.93) P = 0.007**	**0.86(0.75–1.00) P = 0.046**	0.86 (0.71–1.06) P = 0.16	**0.85(0.74–0.97) P = 0.02**
Semaglutide OW	**SUSTAIN-6** (Reference[65])	3297	2.1	8.7%	**0.74(0.58–0.95) P = 0.016**	0.98(0.65–1.48) P = 0.92	0.81(0.57–1.16) P = 0.26	0.65(0.41–1.03) P = 0.066	1.05(0.74–1.50) P = 0.79
Oral semaglutide	**PIONEER-6** (Reference[82])	3183	1.3	8.2%	0.79(0.57–1.11) P = 0.17	**0.49(0.27–0.92) P = 0.02**	1.04(0.66–1.66) P = 0.49	0.76(0.37–1.56) P = 0.43	**0.51(0.31–0.84) P = 0.008**
Exenatide OW	**EXSCEL** (Reference[67])	14752	3.2	8.0%	0.91(0.83–1.00) P = 0.061	0.88(0.76–1.02) P = 0.096	0.97(0.85–1.10) P = 0.62	0.85(0.70–1.03) P = 0.095	**0.86(0.77–0.97) P = 0.016**
Albiglutide OW	**HARMONY OUTCOMES** (Reference[63])	9463	1.6	8.7%	**0.78(0.68–0.90) P = 0.0006**	0.93 (0.79–1.19) P = 0.58	**0.75(0.61–0.90) P = 0.003**	0.86(0.66–1.14) P = 0.30	0.95(0.79–1.01) P = 0.64
Dulaglutide OW	**REWIND** (Reference[65])	9901	5.4	7.2%	**0.88(0.79–0.99) P = 0.03**	0.91(0.78–1.06) P = 0.21	0.96(0.79–1.16) P = 0.63	**0.76(0.62–0.94) P = 0.01**	0.90 (0.80–2.02) P = 0.067
Efpeglenatide	**AMPLITUDE-O** (reference[57])	4075	1.8	8.9%	**0.73 (0.58–0.92) P = 0.007**	0.72 (0.50–1.03) P = 0.07	0.75 (0.54–1.05) P = 0.09	0.74 (0.47–1.17) P = 0.19	0.78 (0.58–1.06) P = 0.11

Cardiovascular Research (2023) 119, 886–904
https://doi.org/10.1093/cvr/cvac112

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Current Agents

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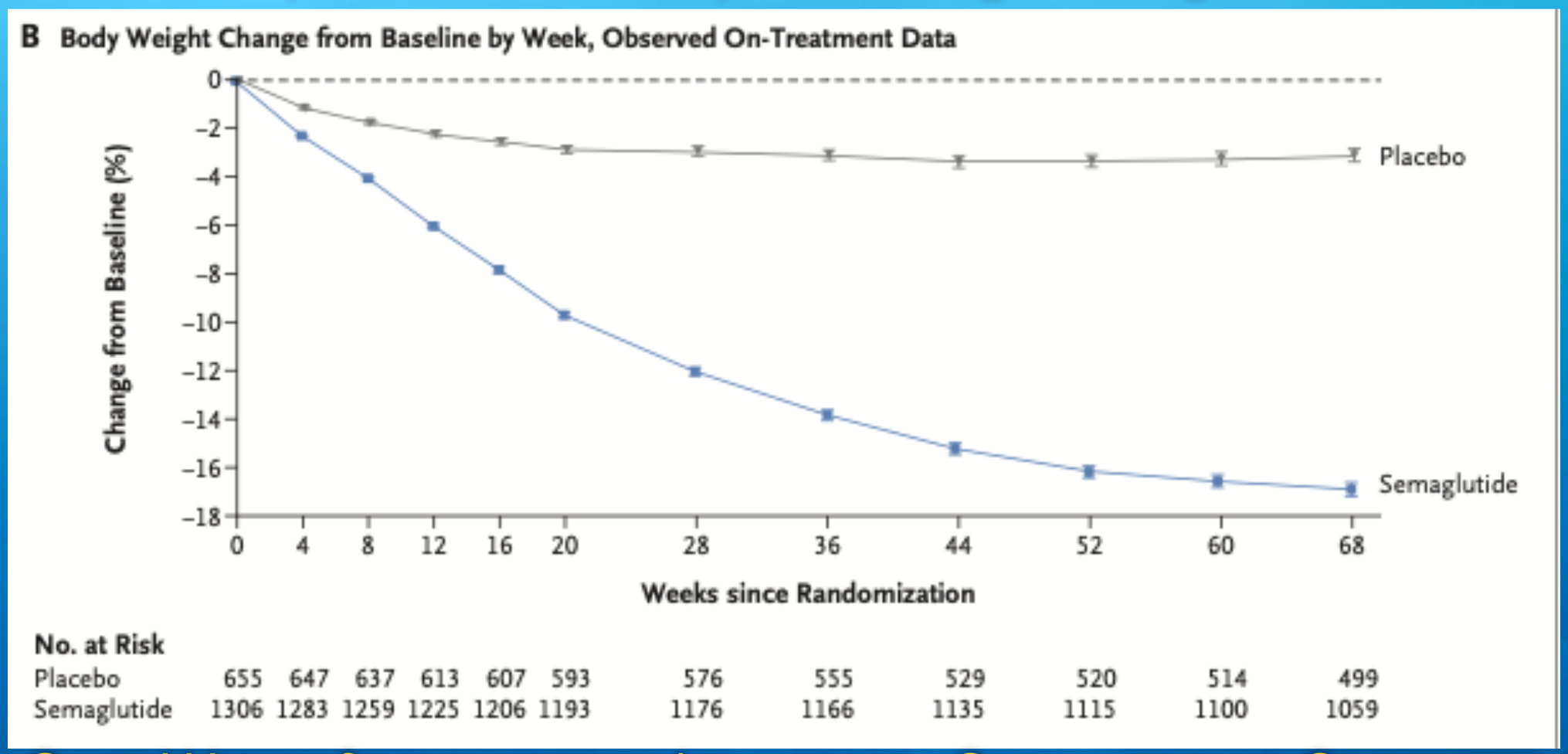
Semaglutide - Prescribing

Once weekly subcutaneous injection 1mg - 2.4mg



Once-Weekly Semaglutide in Adults with Overweight or Obesity

DOI: 10.1056/NEJMoa2032183

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TWINCRETINS - TIRZEPATIDE

Dual agonist at GLP-1 and Glucose dependent insulinotrophic polypeptide (GIP) receptors.

Probably more of a GIP agonist than a GLP-1

Similar safety profile to GLP-1 agonists.

Currently available in vial form - weekly subcutaneous injection:

2.5 mg / **5mg** / 7.5mg / **10mg** / 12.5mg / **15mg**

mounjaro® (tirzepatide) injection

Pricing

Lilly Australia Recommended Retail Prices (RRP) for Mounjaro per 4 vials:[1]

Mounjaro Dose	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg
RRP (for 4 vials)[1]	$315	$315	$515	$515	$645	$645

[1]RRP only. All final pricing at pharmacy discretion.

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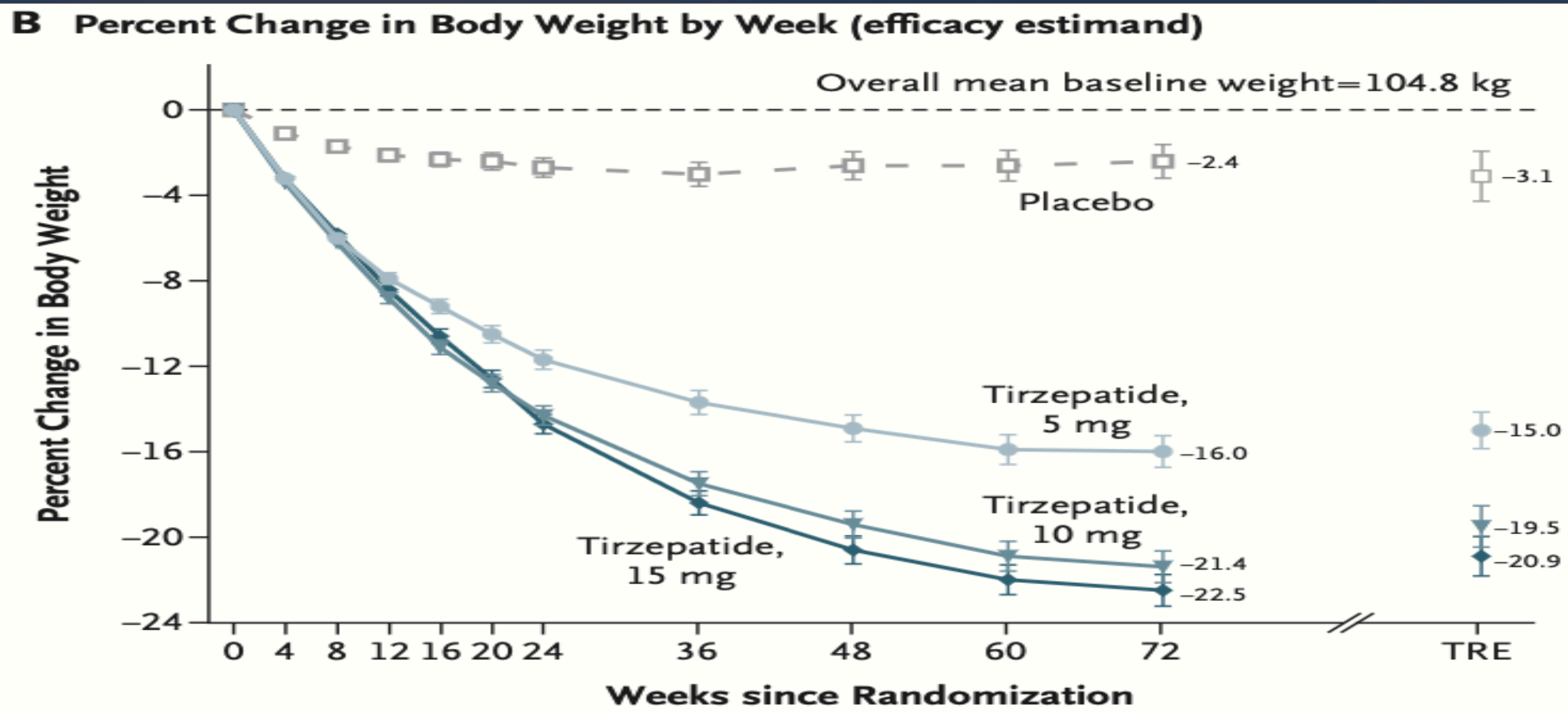
TIRZEPATIDE WEIGHT LOSS



TIRZEPATIDE ONCE WEEKLY FOR THE TREATMENT OF OBESITY
DOI: 10.1056/NEJMOA2206038

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Future developments

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What's in the pipeline

Orforglipron - Non peptide agonist

Retatrutide - Triple G agonist

Other Twincretins (GLP-1/Glucagon)

Amylin agonists

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Orforglipron

Non-peptide GLP-1 Agonist

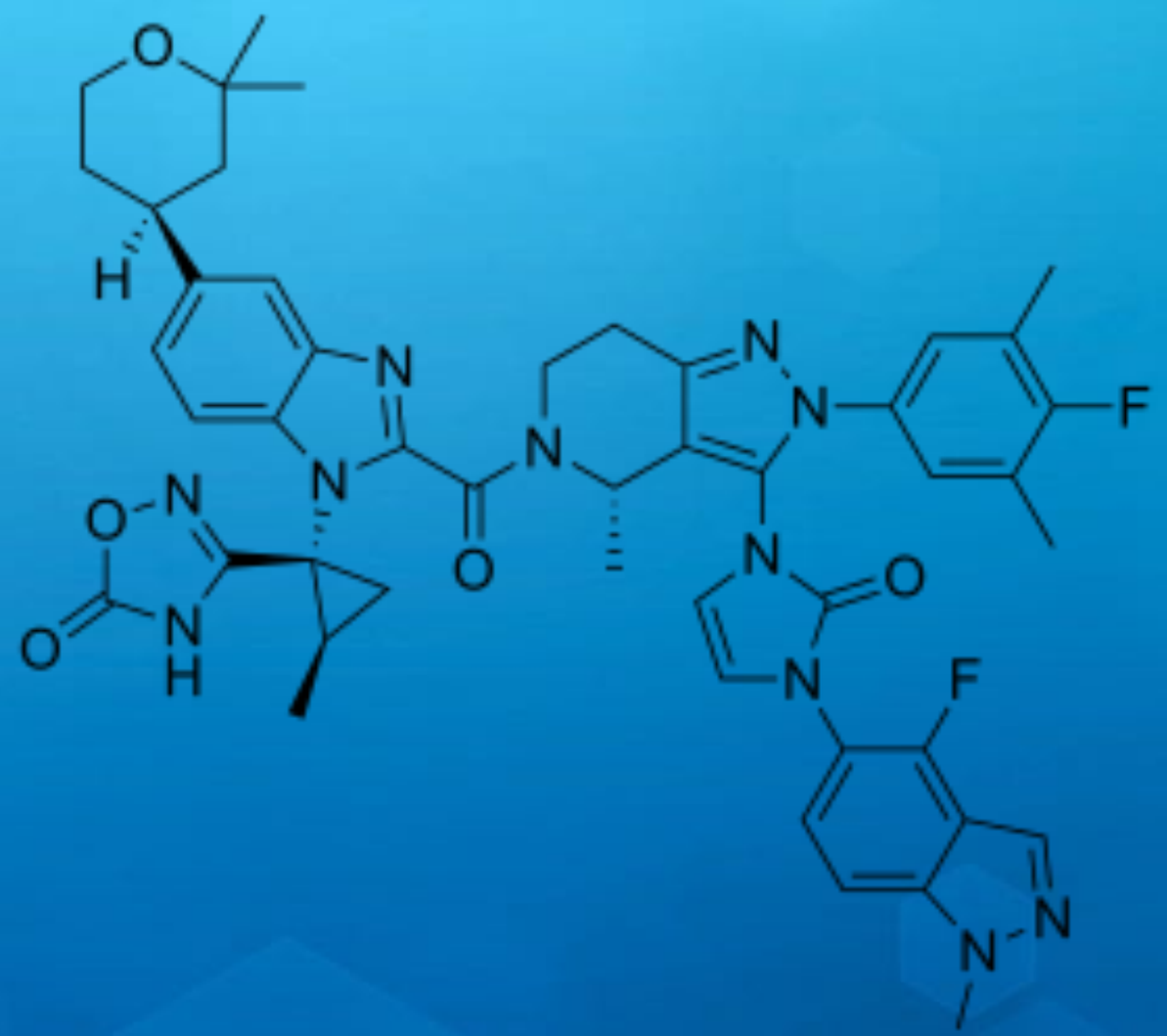
Recently safety trials look promising

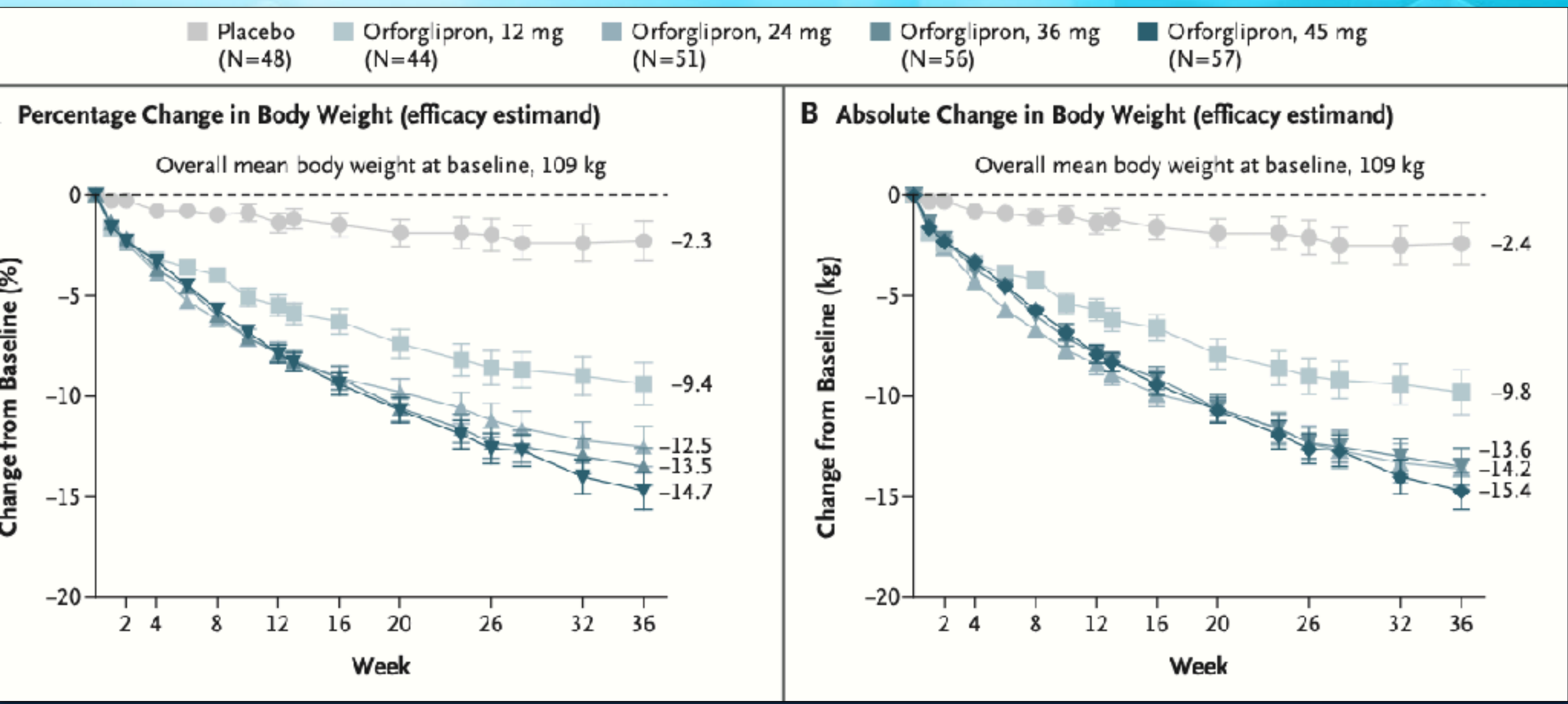
Doesn't need to be refrigerated

Can be taken orally

Half life 29-49 hours

Once daily dose





Orforglipron Weight Loss

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity
DOI: 10.1056/NEJMoa2302392

Retatrutide

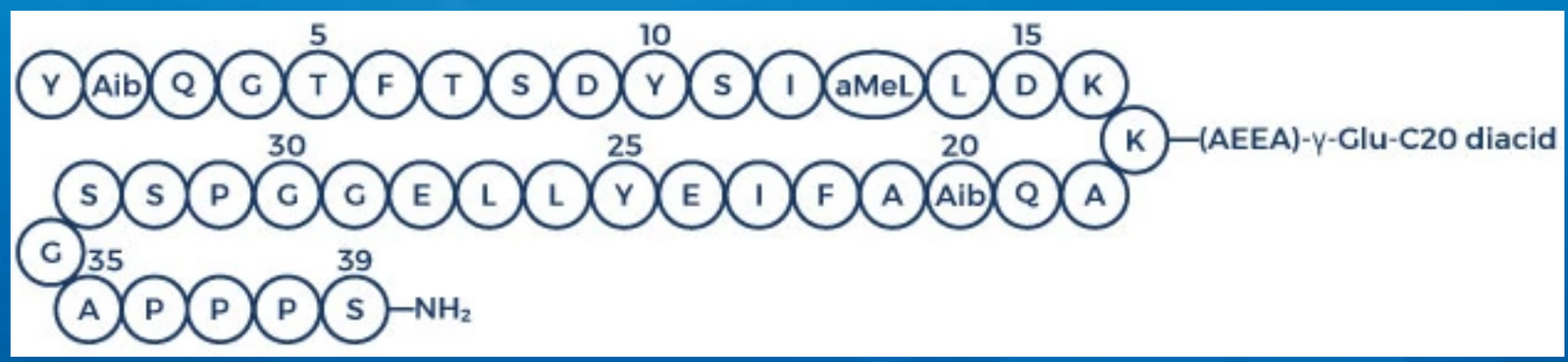
Triple G agonist:

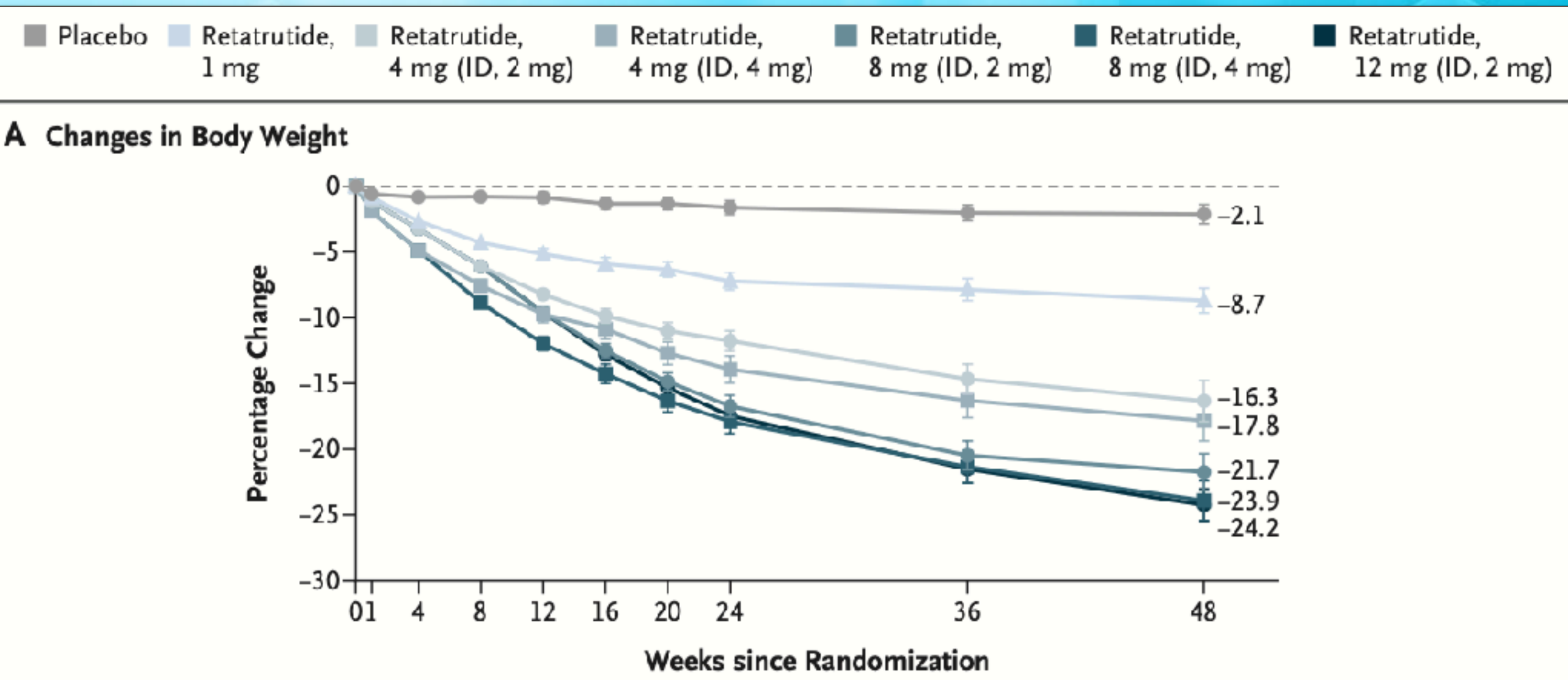
GLP-1, GIP and Glucagon agonist

Higher efficacy in weight loss

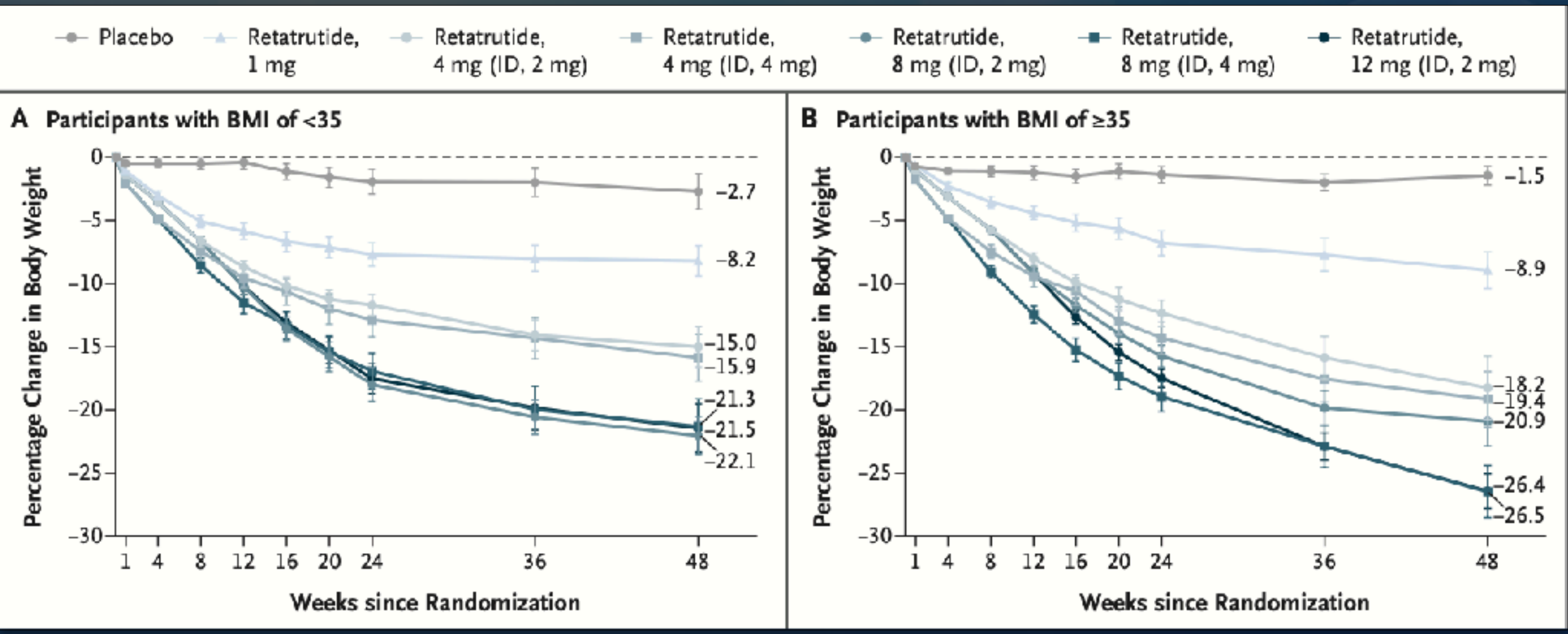
May have more side effects (⬆HR)

Safety profile still appears similar to other incretin therapies





Retatrutide weight loss



Sub group analysis

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial
DOI: 10.1056/NEJMoa2301972

Newer agents

Pemvidutide - GLP-1 and glucagon agonist

- Doesn't reduce blood glucose
- Causes weight loss, lipid reductions and improves non-alcoholic fatty liver
- Has passed phase 1 trials.
  - 9-10% body weight loss at 12 weeks.

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CagriSema

Combination of Semaglutide with Cagrilintide (Amylin agonist)

Very effective control of blood glucose - 75% achieved HbA1C < 6.5%

Higher rates of adverse gastrointestinal events, usually mild

Improvement in blood pressure, lipids and CRP

Weight loss at 32 weeks 15.6% TBW

Compared with semaglutide 2.4mg weekly alone 5.1% TBW

Cagrilintide is also a calcitonin receptor agonist

Summary

- Conventional approach to weight management
- Incretin therapies
- Current agents
- Future developments