

Weight reduction to Reduce CV Mortality in Overweight/Obese CVD patients

Asst. Prof. Patchaya Boonchaya-anant, MD

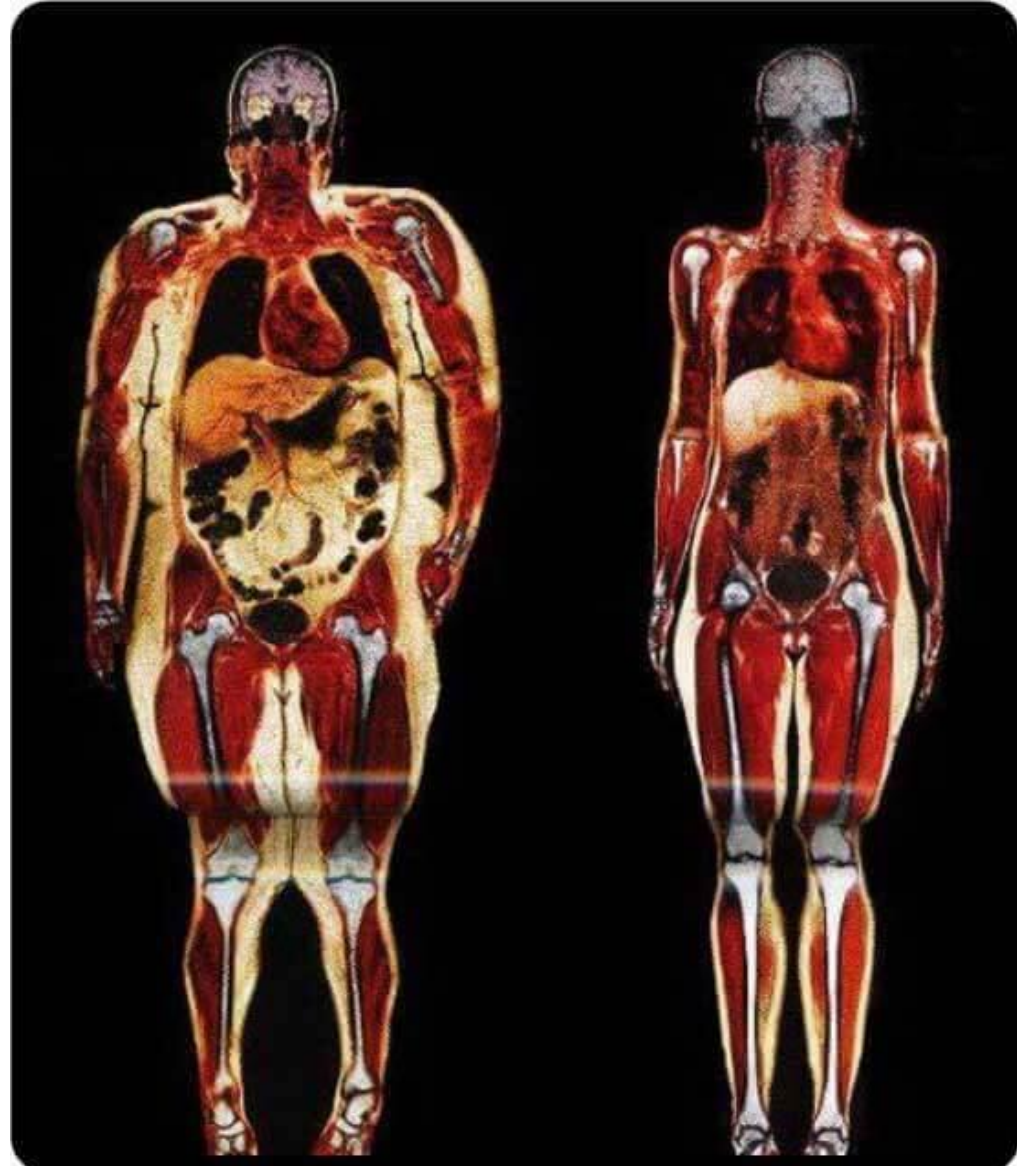


Outline

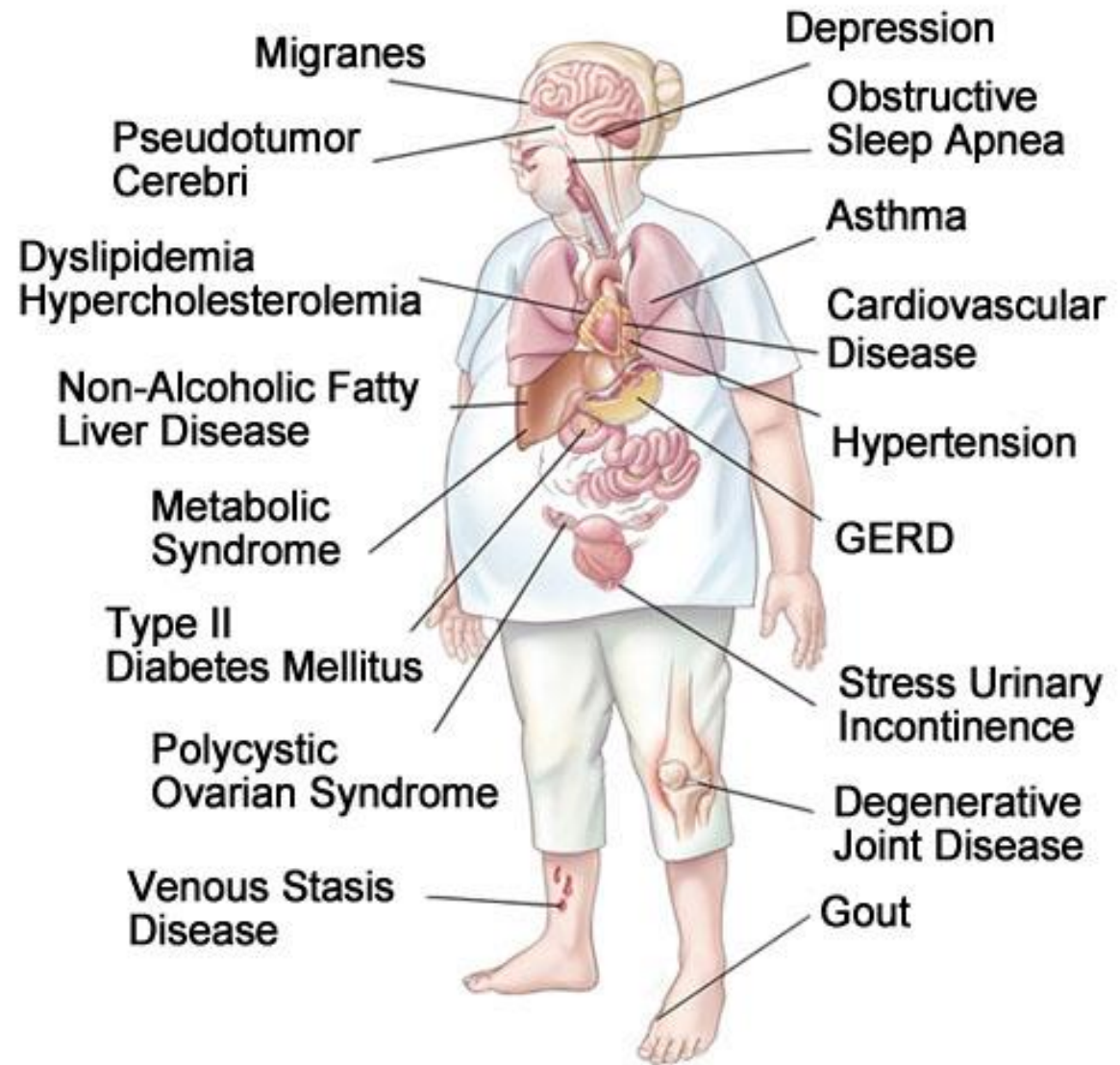
- **Obesity and CVD**
- **Weight loss interventions**
 - **Lifestyle interventions**
 - **Obesity pharmacotherapy**
 - **Bariatric surgery**

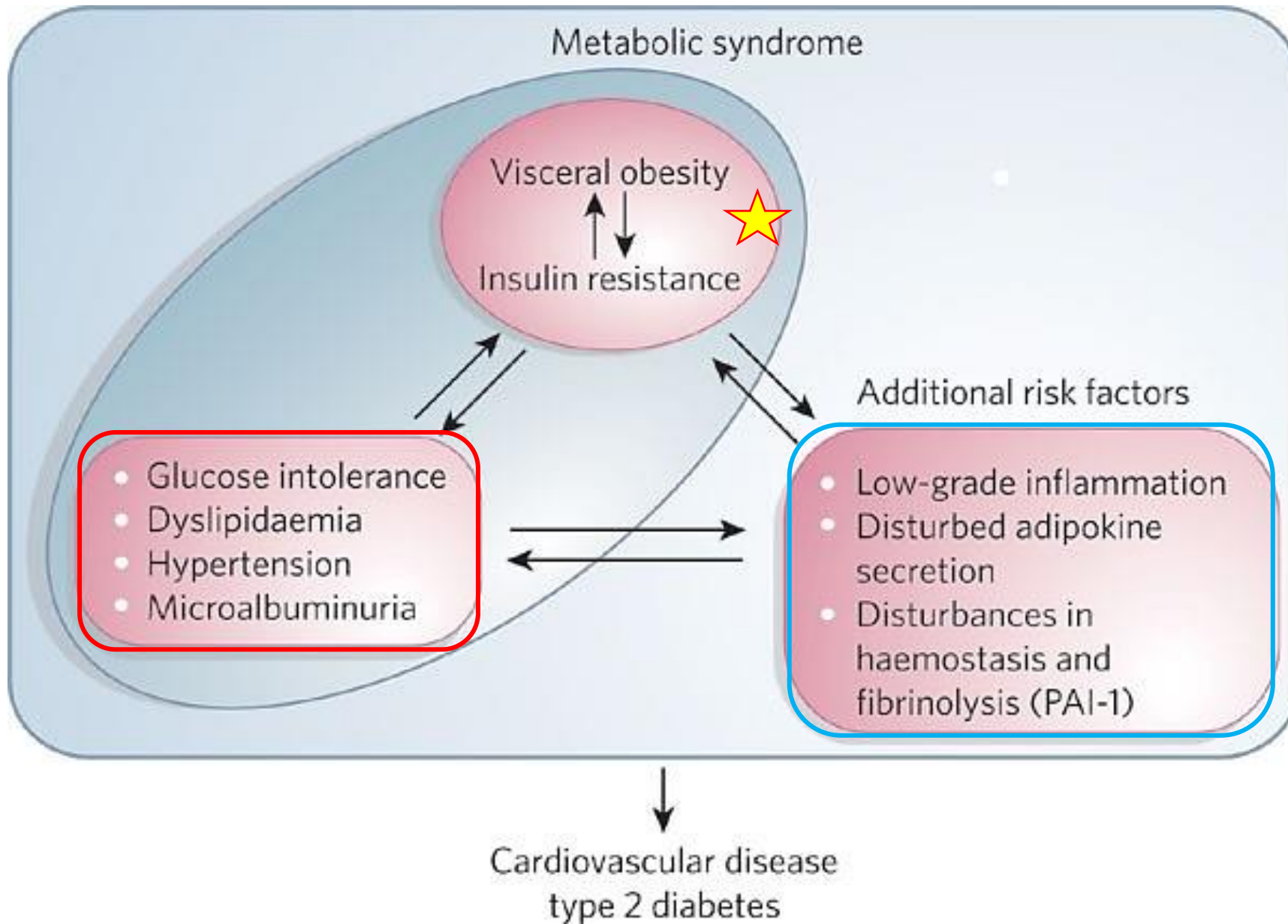


Obesity =
Excess fat
(adipose
tissue)

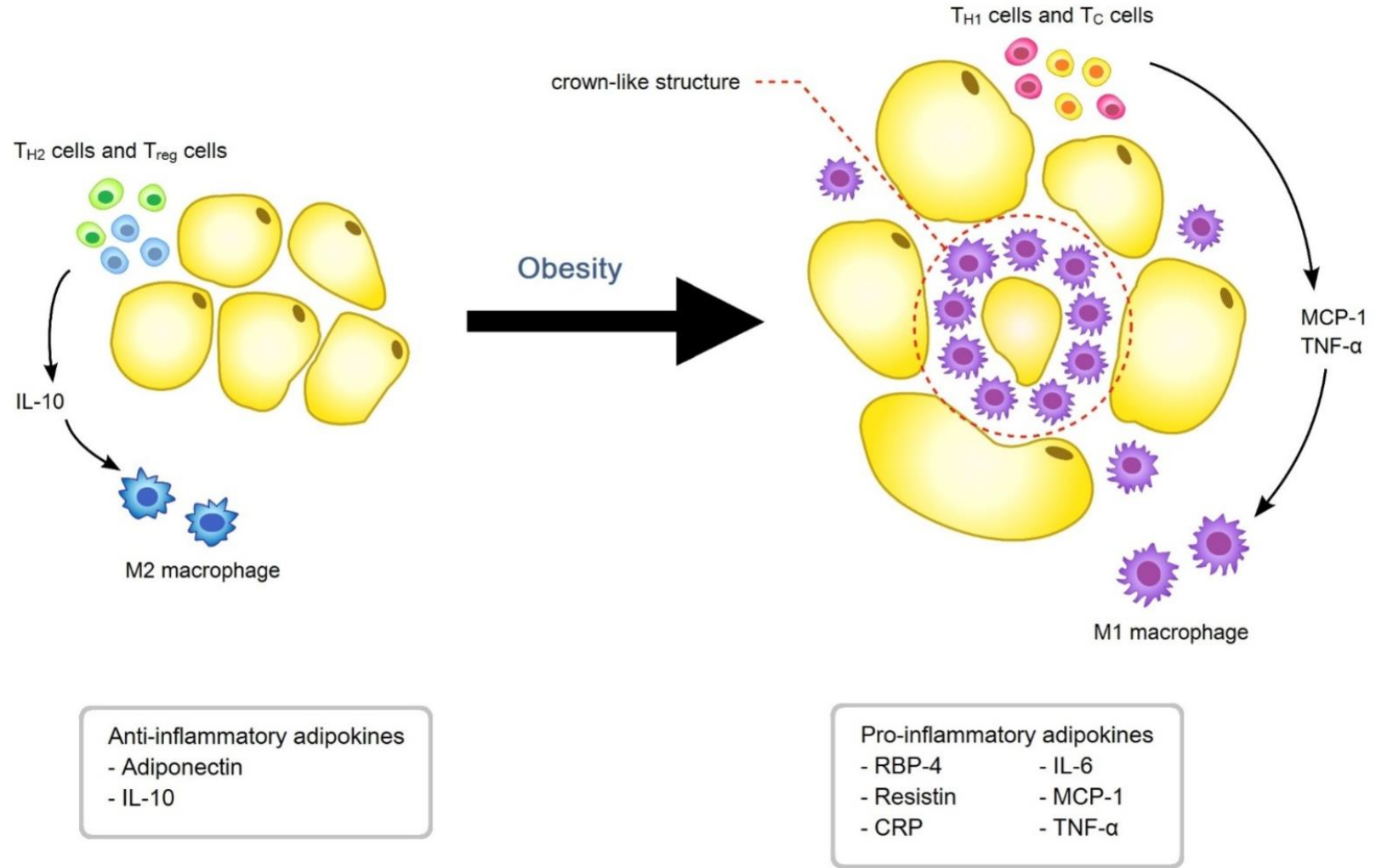


Obesity-related comorbidities

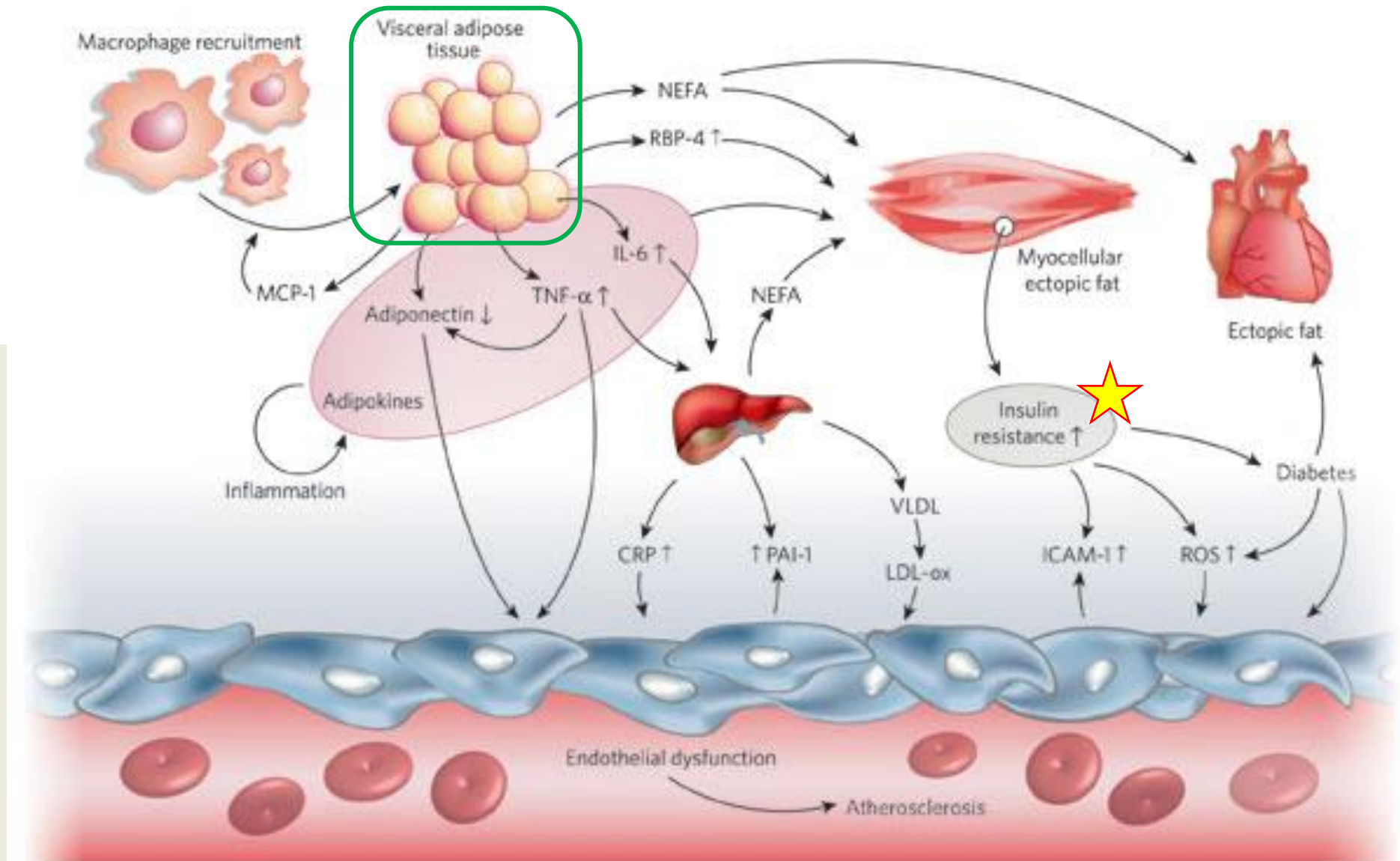




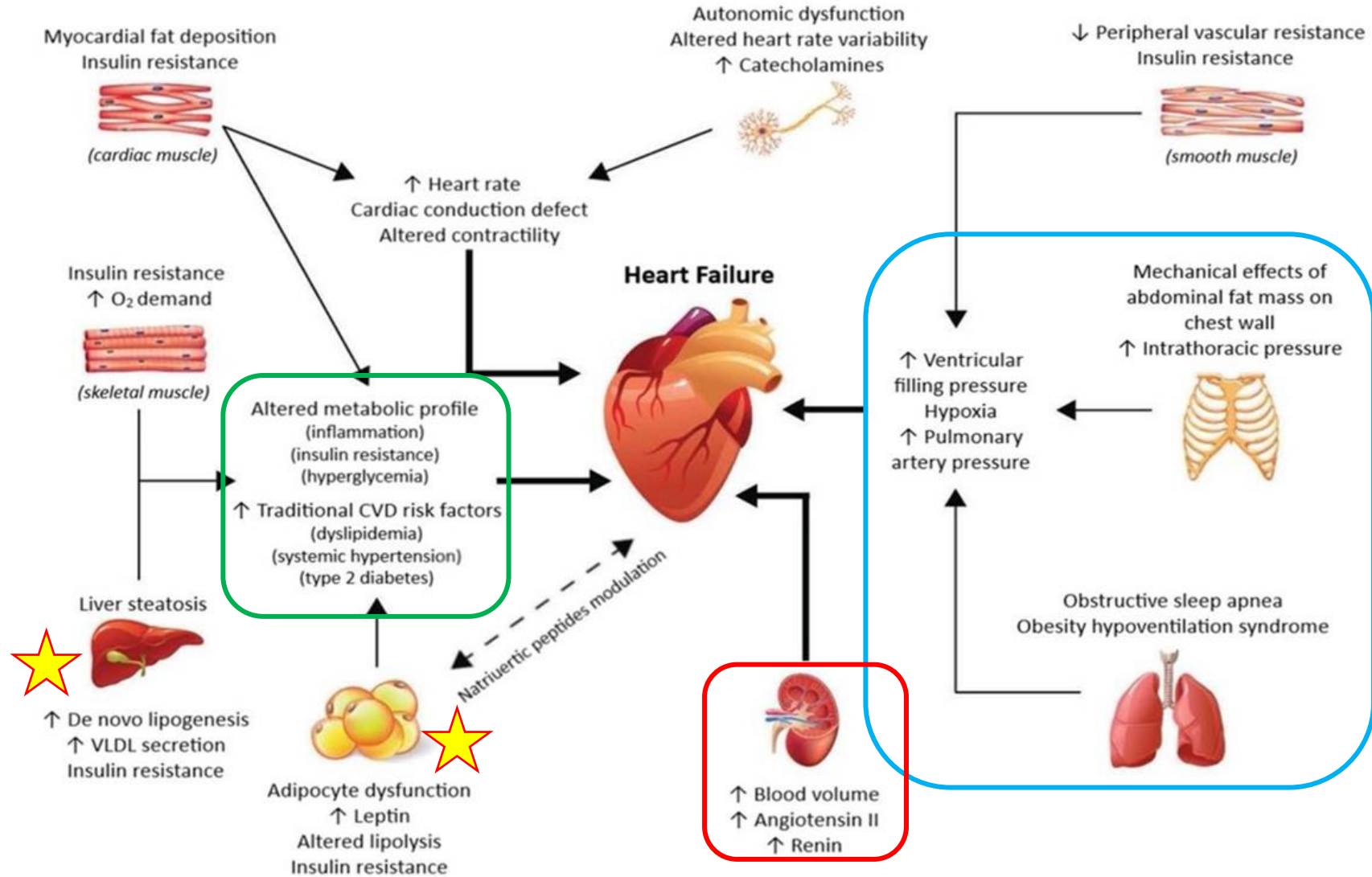
Fat and inflammation



Abdominal (visceral) fat and insulin resistance may contribute to cardiovascular disease



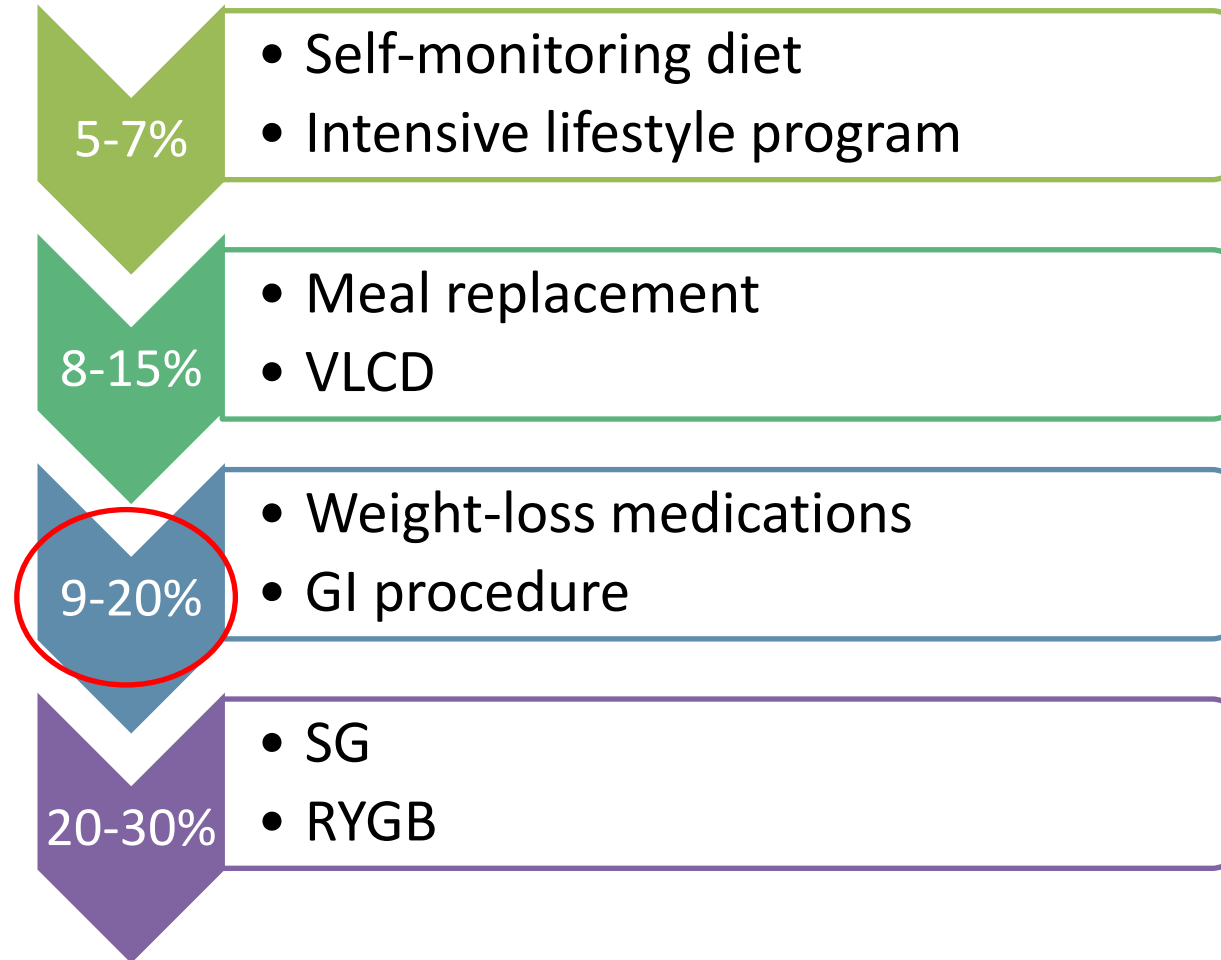
Obesity is associate with HFpEF

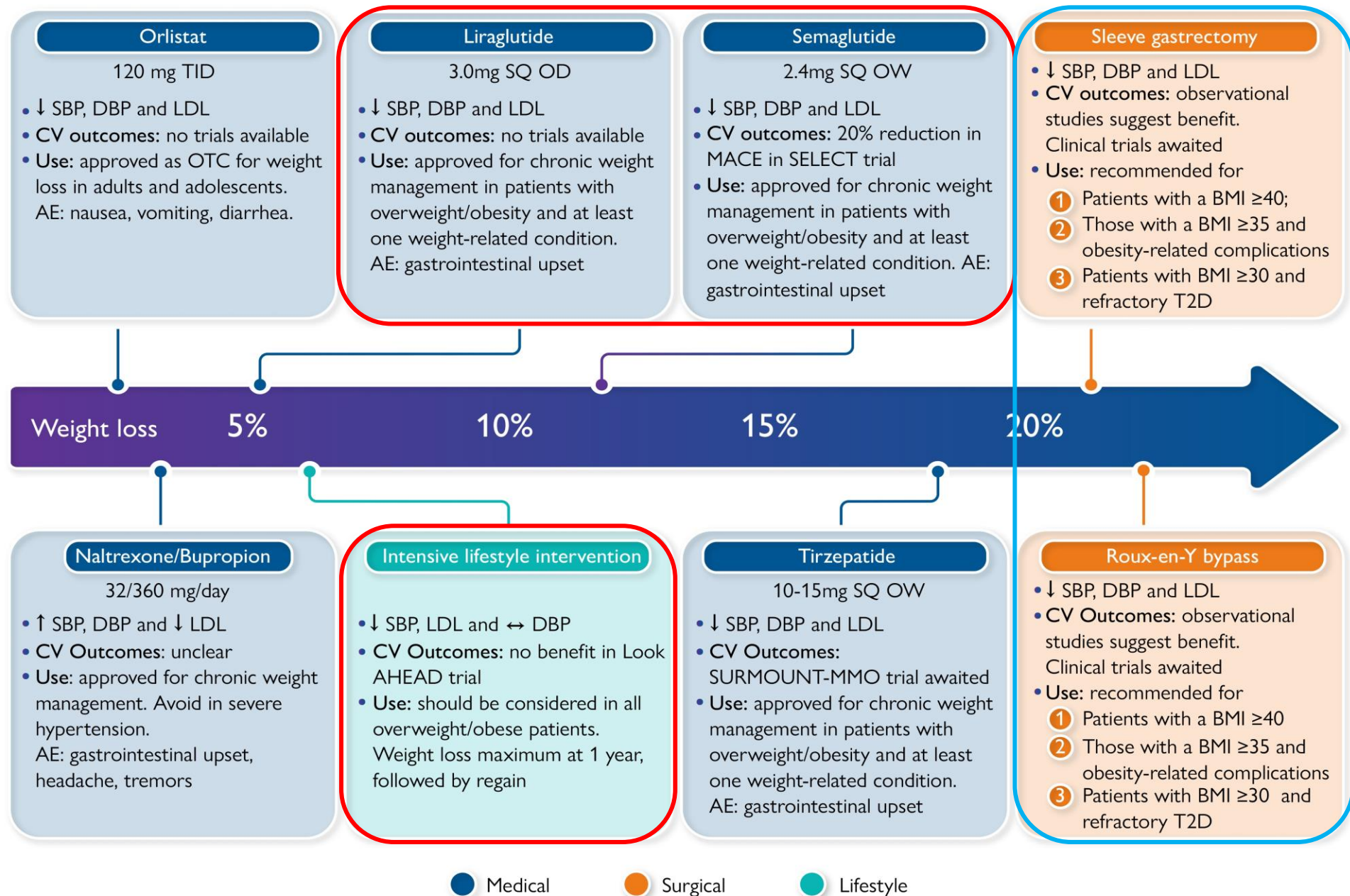


A close-up photograph of a purple fabric with a black and white checkered pattern. The fabric is draped and folded, creating deep shadows and bright highlights. The word "Treatment" is overlaid in the center in a white, sans-serif font.

Treatment

Treatment effectiveness (%BW loss)

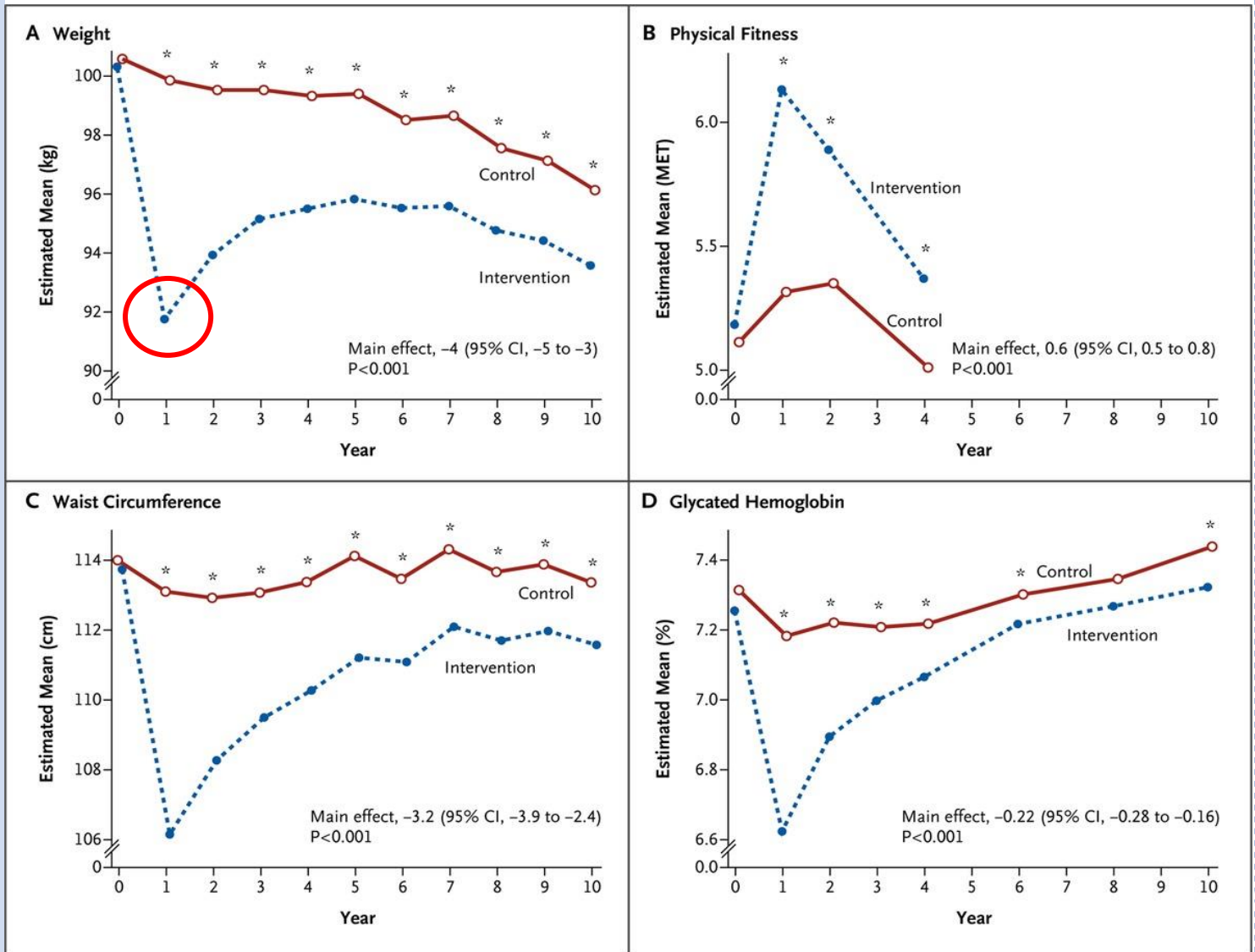




Look AHEAD trial

- DM + overweight/obese
- ITL : 3 group + 1 individual session /month x 6 months
 - → 7-10% BW loss
- **Improvement in glucose, lipids, BP, OSA, NAFLD, depression, incontinence, QOL, sexual function and etc.**
- **Reduced No. of meds, DM remission**
- *No difference in cardiovascular endpoints (very low event rate)*

The Look AHEAD: 10 Years of Follow-up

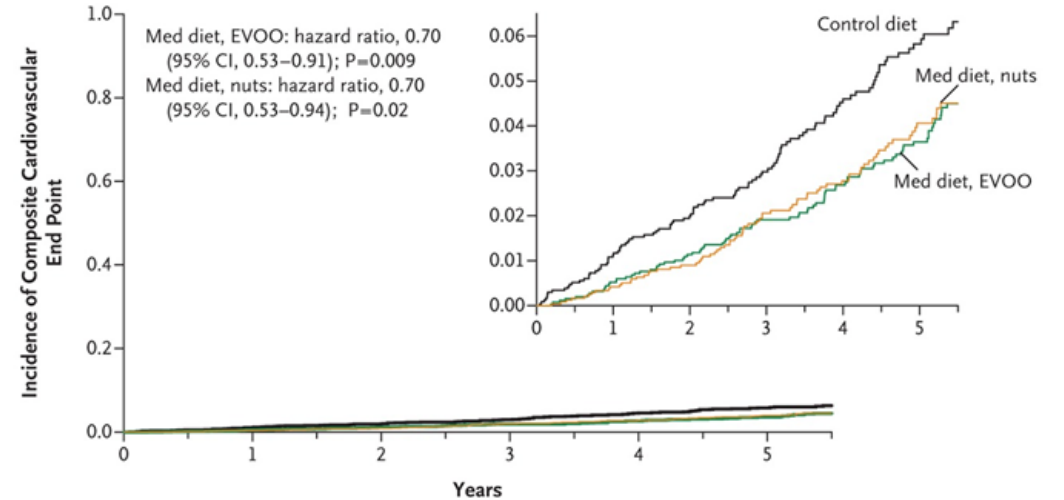


the PREDIMED Study

Mediterranean diet

Mean BMI 29-30 kg/m²

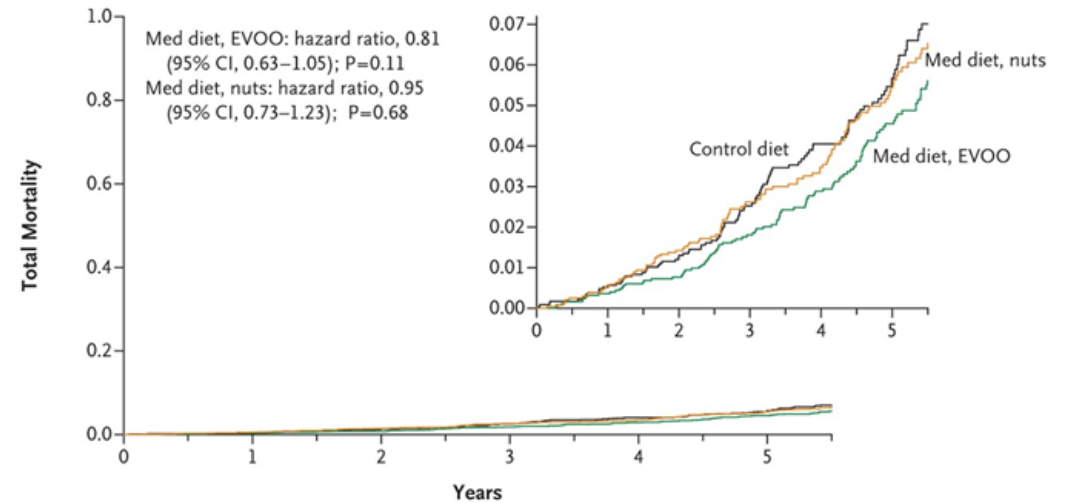
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

B Total Mortality



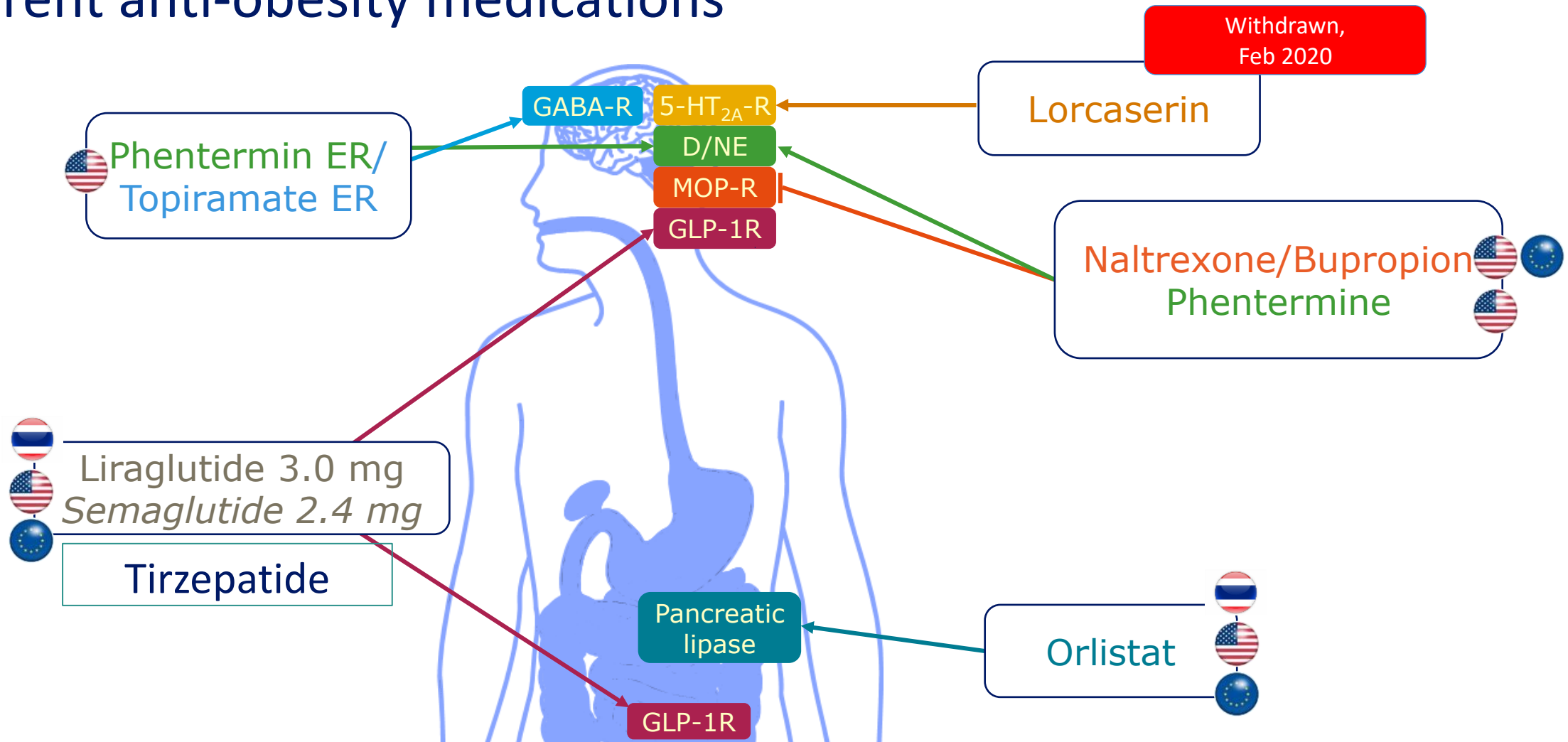
No. at Risk

Control diet	2450	2268	2026	1585	1272	948
Med diet, EVOO	2543	2485	2322	1988	1690	1308
Med diet, nuts	2454	2345	2097	1662	1395	1037



Obesity Pharmacotherapy

Current anti-obesity medications



Lorcaserin and phentermine/topiramate are not approved for weight management in the EU.

5-HT_{2A}-R, 5-hydroxytryptamine 2A receptor; D, dopamine; GABA-R, gamma-aminobutyric acid receptor; GLP-1R, glucagon-like peptide-1 receptor;

MOP-R, mu opioid receptor; NE, norepinephrine; WL, weight loss.

Patel. *Metabolism* 2015;64:1376–85; FDA approved drugs available at: <http://www.fda.gov/Drugs/default.htm>. Last accessed August 2019; EMA approved drugs. Available at: <http://www.ema.europa.eu/>. Last accessed August 2019.

FDA draft guidance

Clinical trial criteria to demonstrate the efficacy of weight loss medication (based on 2007 draft guidance)

Population:

- Significant risk for weight-related morbidity and mortality
- BMI ≥ 30 kg/m², or
- BMI ≥ 27 kg/m² + comorbidities
 - Type 2 diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease

Size/duration (safety):







- n $\geq 3,000$ (active), n $\geq 1,500$ (placebo)
- 1 year

Efficacy:

- Placebo-adjusted mean weight loss $\geq 5\%$, or
- $\geq 35\%$ achieving $\geq 5\%$ weight loss and twice that of placebo

Expected effects of weight loss interventions on cardiovascular risk factors

Intervention	Heart Rate	Systolic Blood Pressure	Diastolic Blood Pressure	LDL	HDL	Triglycerides
Intensive lifestyle intervention	?	↓	↔	↔	↑	↔
Liraglutide 3mg SQ OD	↑	↓	↓	↓	↑	↓
Semaglutide 2.4mg SQ OW	↑	↓	↓	↓	↑	↓
Tirzepatide 5-15mg SQ OW	↑	↓	↓	↓	↑	↓
Diethylpropion 50 mg BID	↔	↔	↔	↔	↔	↓
Naltrexone/Bupropion	↑	↑	↑	↓	↑	↓
Orlistat 120mg TID	↔	↓	↓	↓	↔	↔
Sleeve gastrectomy	↓	↓	↓	↓	↑	↓
Roux-en-Y bypass	↓	↓	↓	↓	↑	↓

 Potential decrease
  Potential increase
  No/minimal change likely
  Beneficial change
  Deleterious change
  Unknown effect

Indication and dosing

Diabetes

- Liraglutide 1.8 mg daily
- Semaglutide 1.0 mg wkly

LEADER

SUSTAIN-6

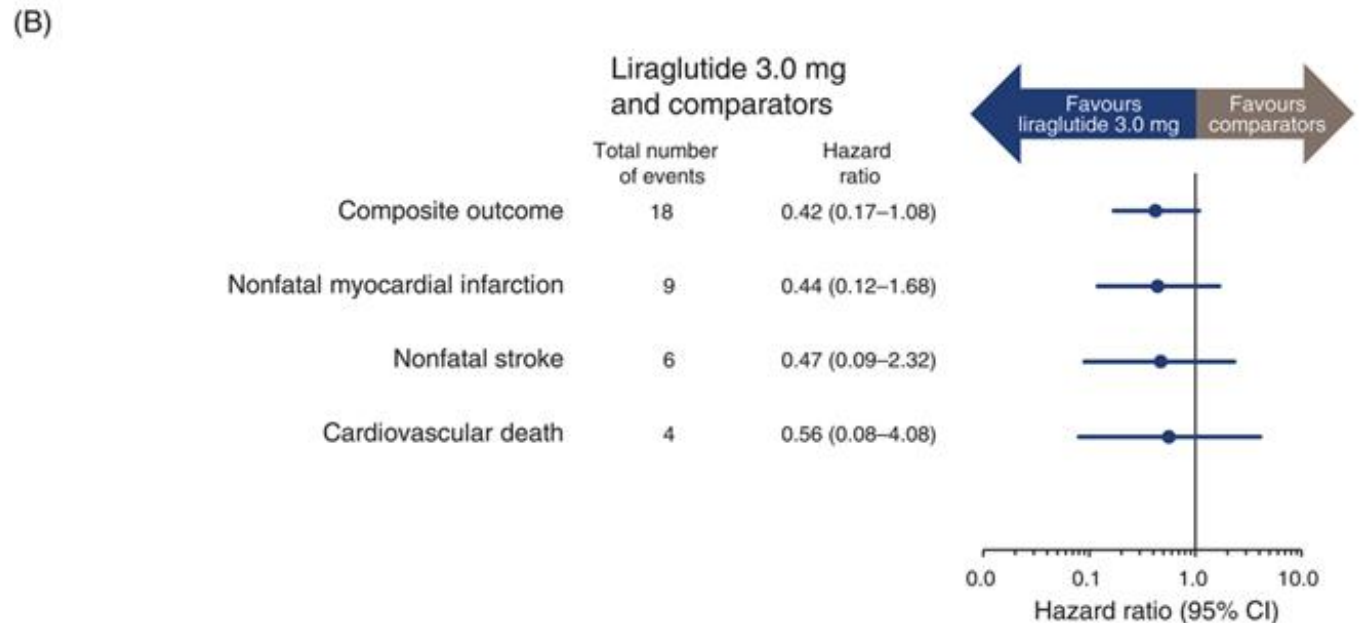
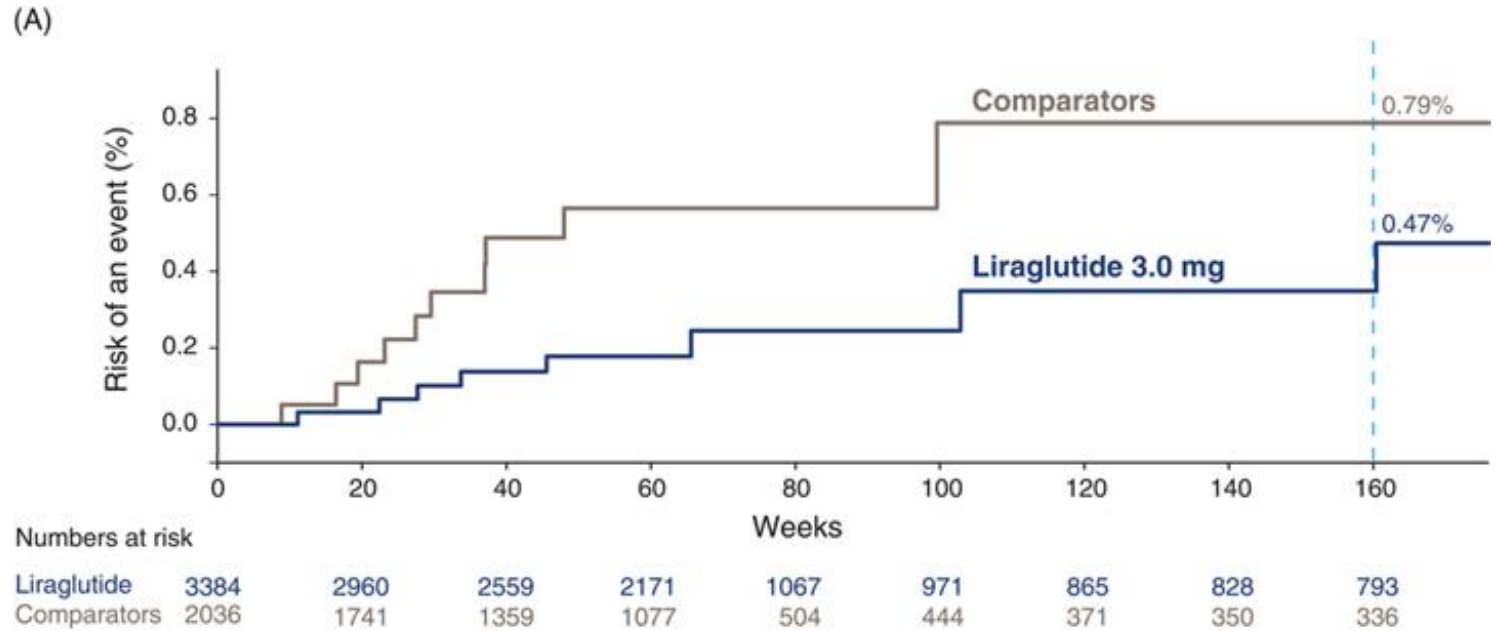
Obesity

- Liraglutide 3 mg daily
- Semaglutide 2.4 mg wkly

post hoc analysis
from SCALE

SELECT

Liraglutide and CV outcomes in adults with overweight or obesity: A post hoc analysis from SCALE RCTs



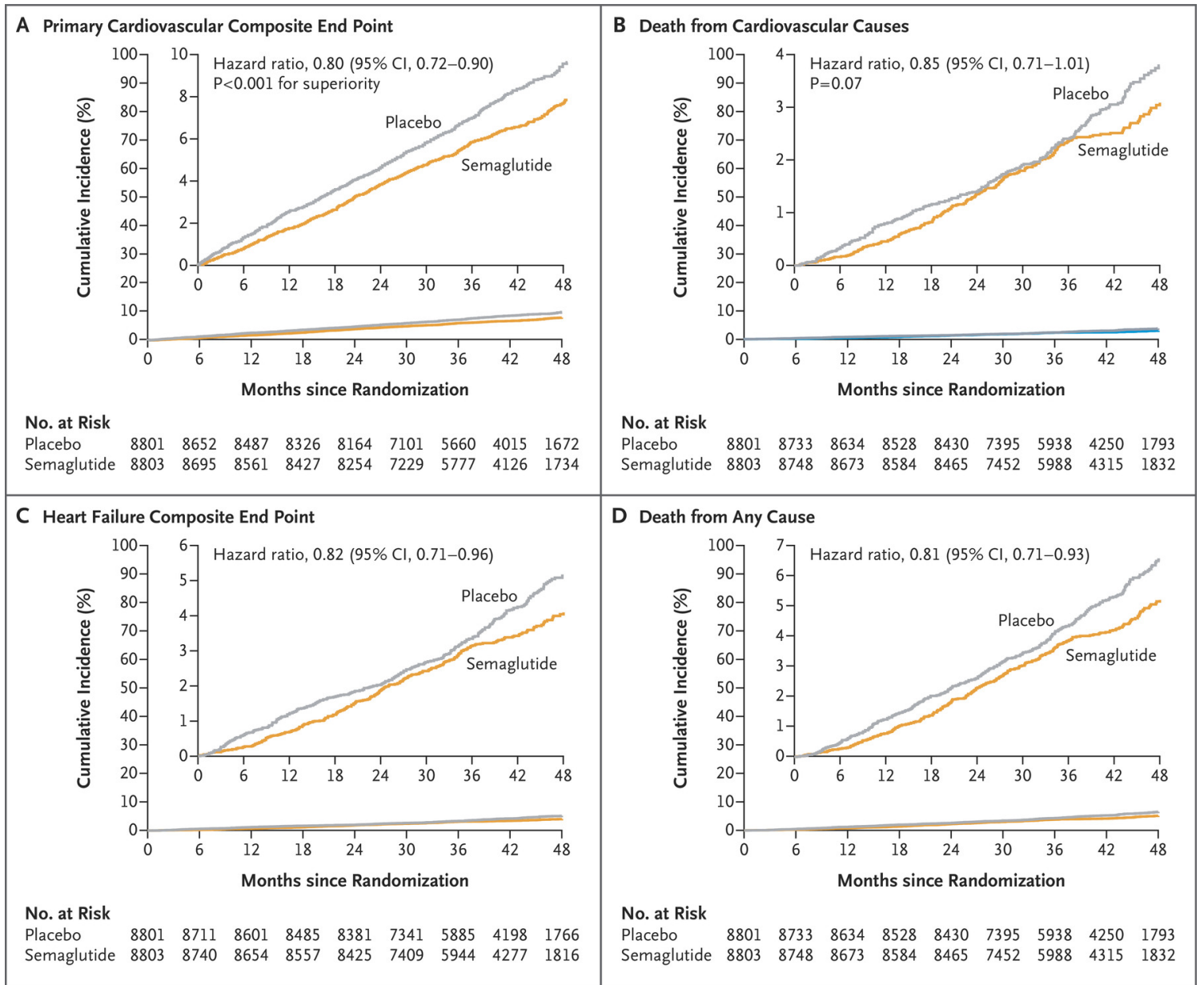
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT)

Mean weight loss 9.4%

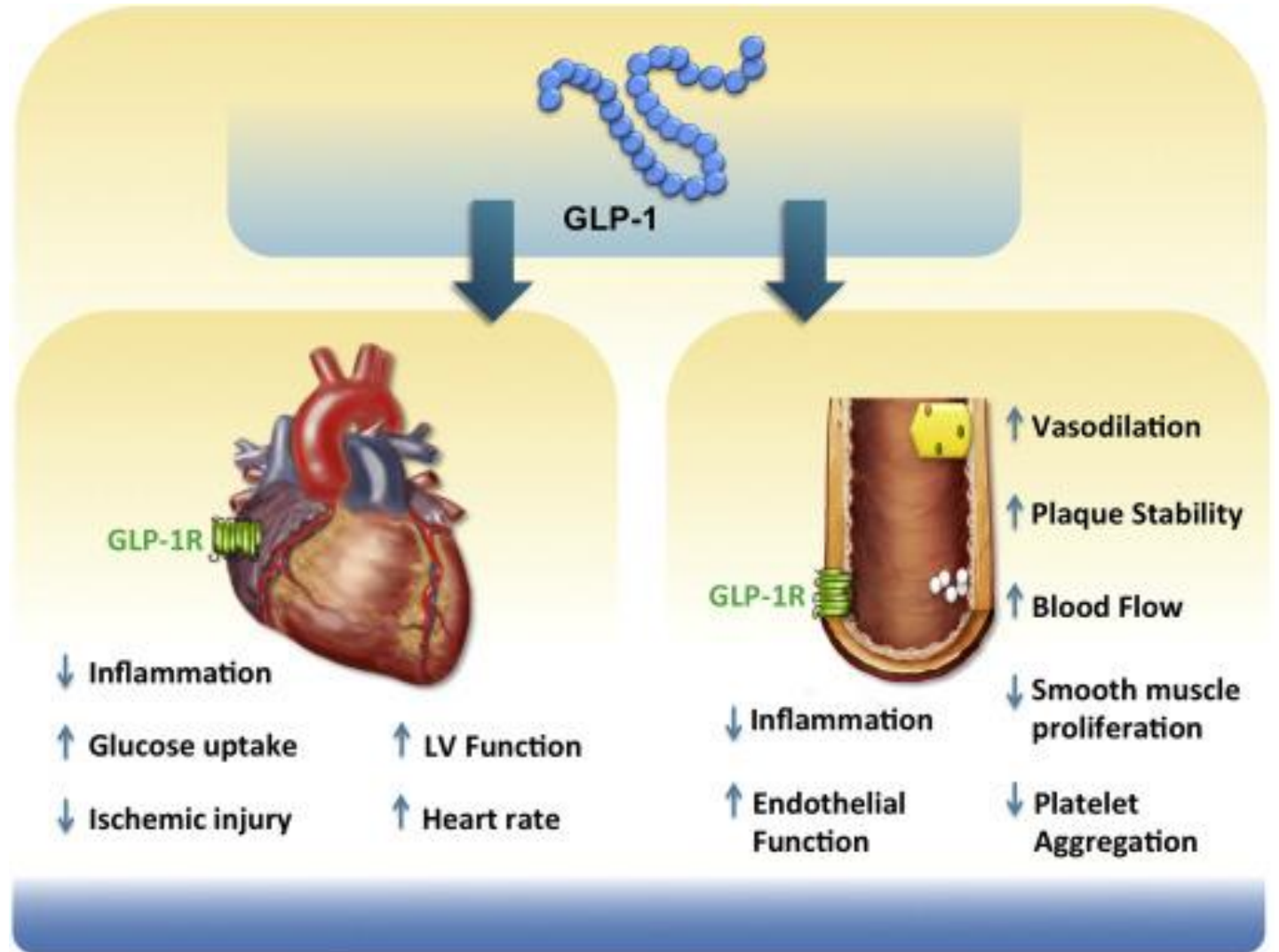
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N = 8803)	Placebo (N = 8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)

Is it due to the weight loss or GLP1RA itself?



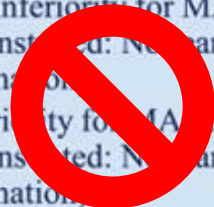
Mechanisms of GLP-1 receptor agonist



Cardiovascular outcome trials in obesity

The Light Study⁵³

- 8,910 participants
- Naltrexone–bupropion (32 mg/360 mg, n=4,455) vs placebo (n=4,450)
- Median BMI, 36.6; 32.1% with CVD; 85.2% with diabetes
- 2.3 years' duration
- Result of primary outcome (3-point MACE), HR [95% CI]: 0.88 [0.57; 1.34]
- Non-inferiority for MACE demonstrated: No (early trial termination)
- Superiority for MACE demonstrated: No (early trial termination)

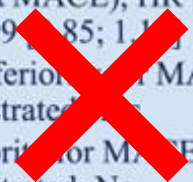


AQCLAIM⁵⁴

- 16,000 participants
- Phentermine/topiramate (15/92 mg/day) vs placebo
- ~4 years' duration
- No result (trial not yet started)
- Non-inferiority for MACE demonstrated: No (trial not yet started)
- Superiority for MACE demonstrated: No (trial not yet started)

CAMELLIA-TIMI 61⁵⁵

- 12,000 participants
- Lorcaserin (10 mg twice daily, n=6,000) vs placebo (n=6,000)
- Median BMI, 35; 74.7% atherosclerotic CVD; 56.8% diabetes; 90.4% hypertension; 93.6% hyperlipidaemia; 19.0% chronic kidney disease
- 3.3 years' duration
- Result of primary outcome (3-point MACE), HR [95% CI]: 0.99 [0.85; 1.14]
- Non-inferiority for MACE demonstrated: No
- Superiority for MACE demonstrated: No

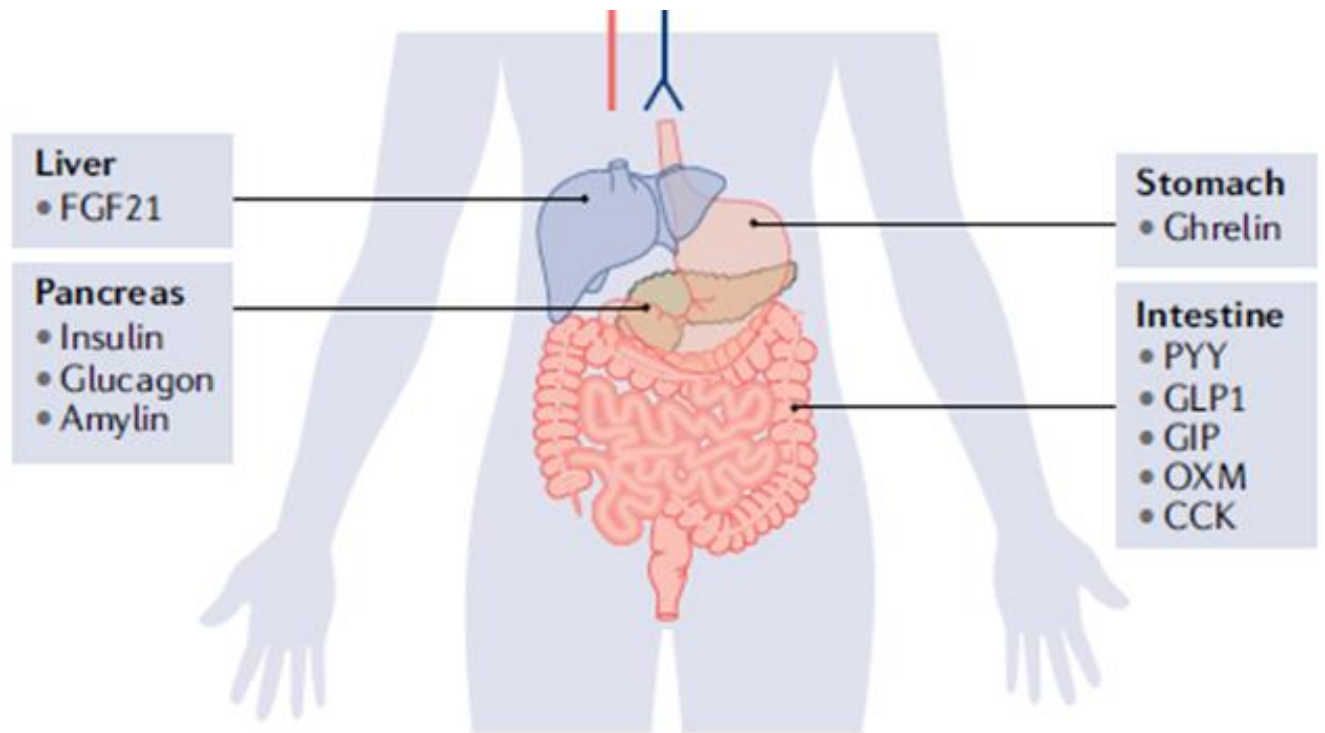


SELECT⁵⁶

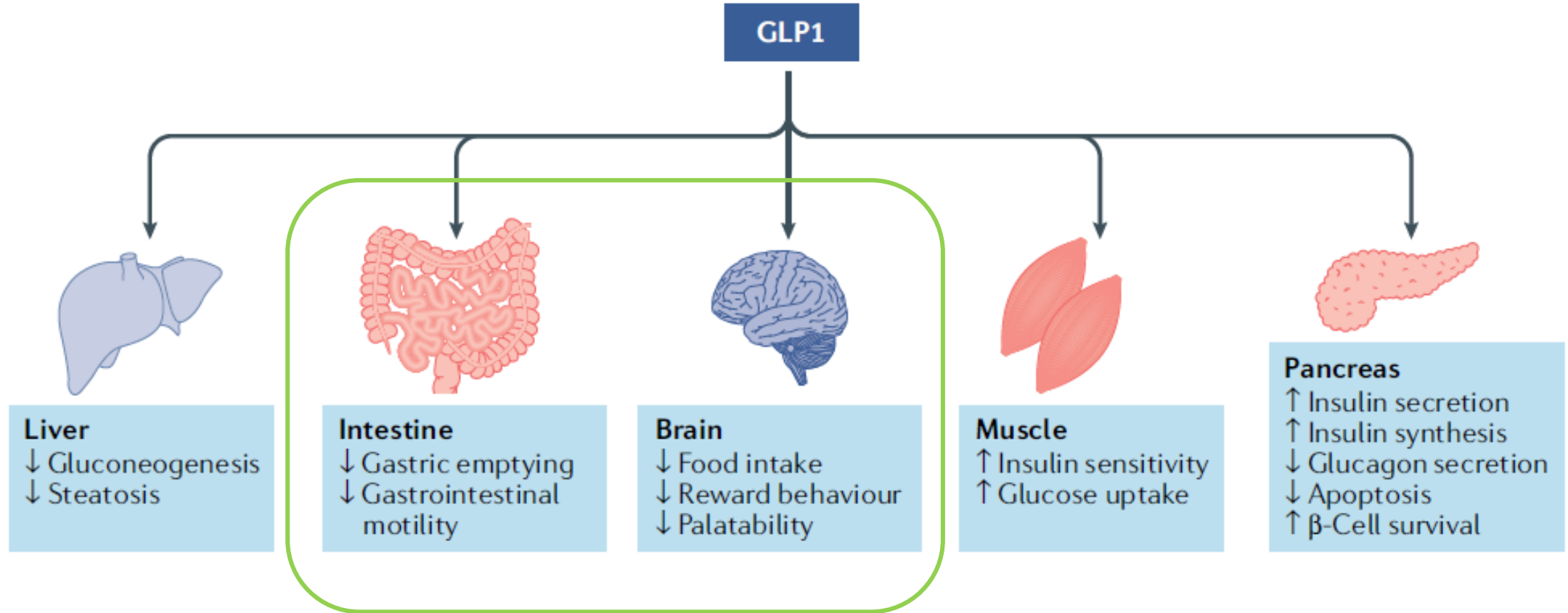
- Aims to enrol 17,500 participants
- Semaglutide 2.4 mg vs placebo
- ~5 years' duration
- No results yet (trial ongoing)



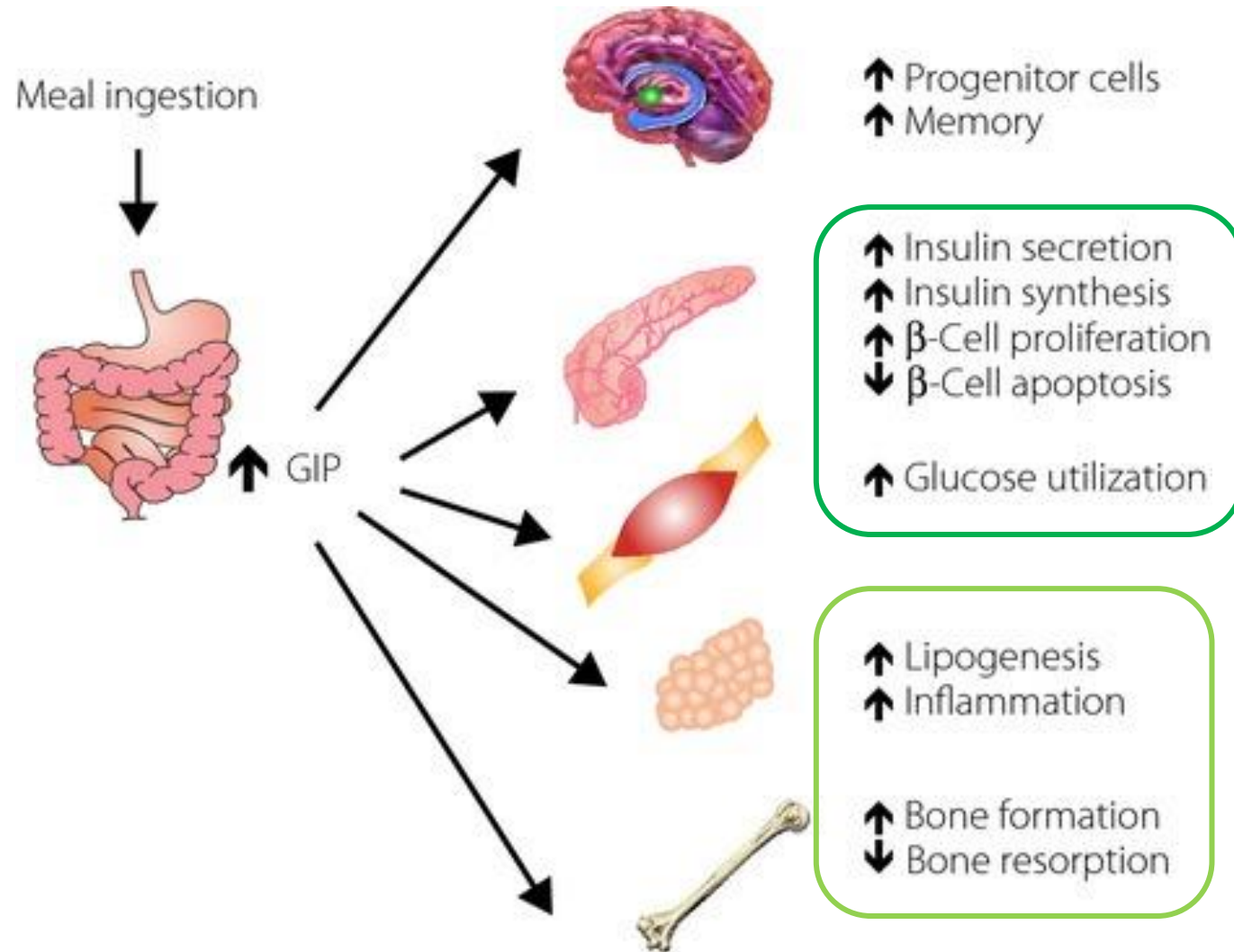
Let's learn more about our gut hormones



GLP-1 = Glucagon-like peptide-1



GIP = Glucose dependent Insulinotropic Polypeptide



Glucagon-like Peptide-1 Receptor Agonism

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System

- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas

- ↑ Insulin
- ↓ Glucagon

Stomach

- ↓ Gastric Emptying

Systemic

- ↓ Hyperglycemia

Liver

- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

Central Nervous System

- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas

- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue

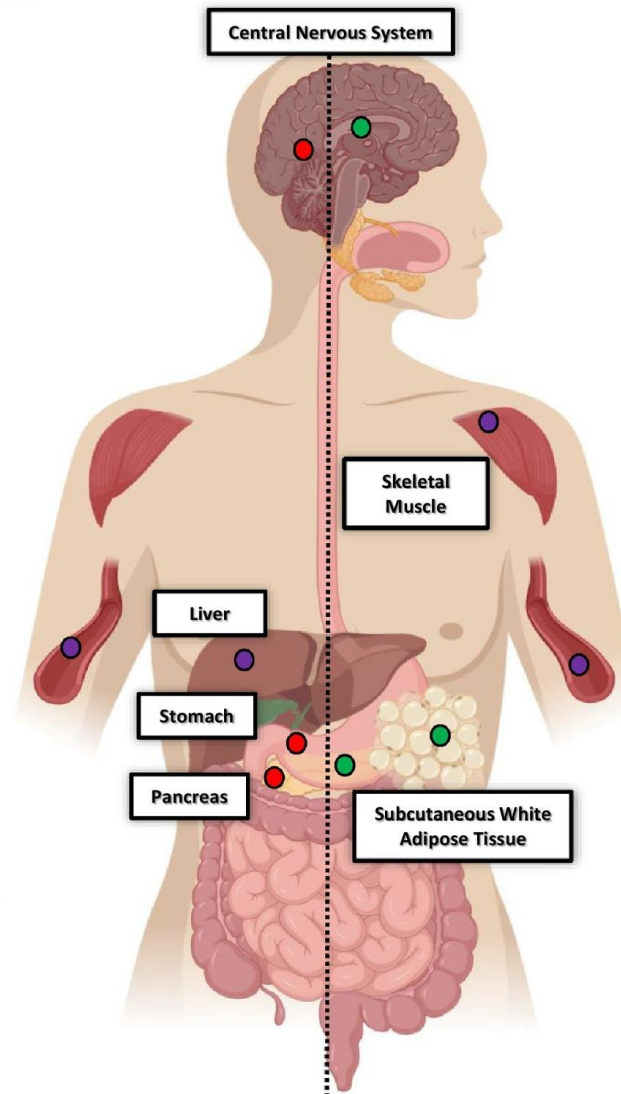
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic

- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle

- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

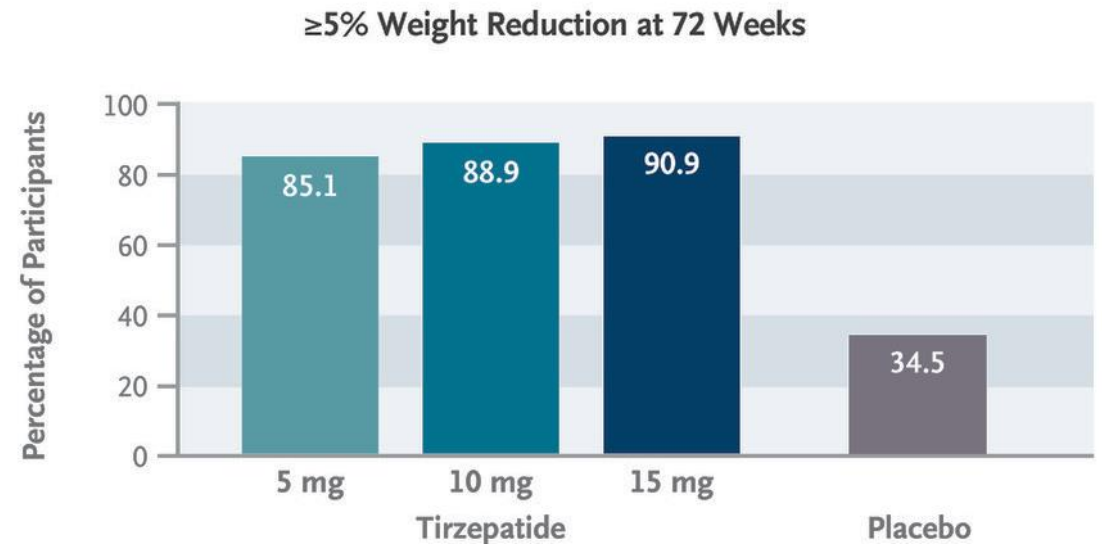
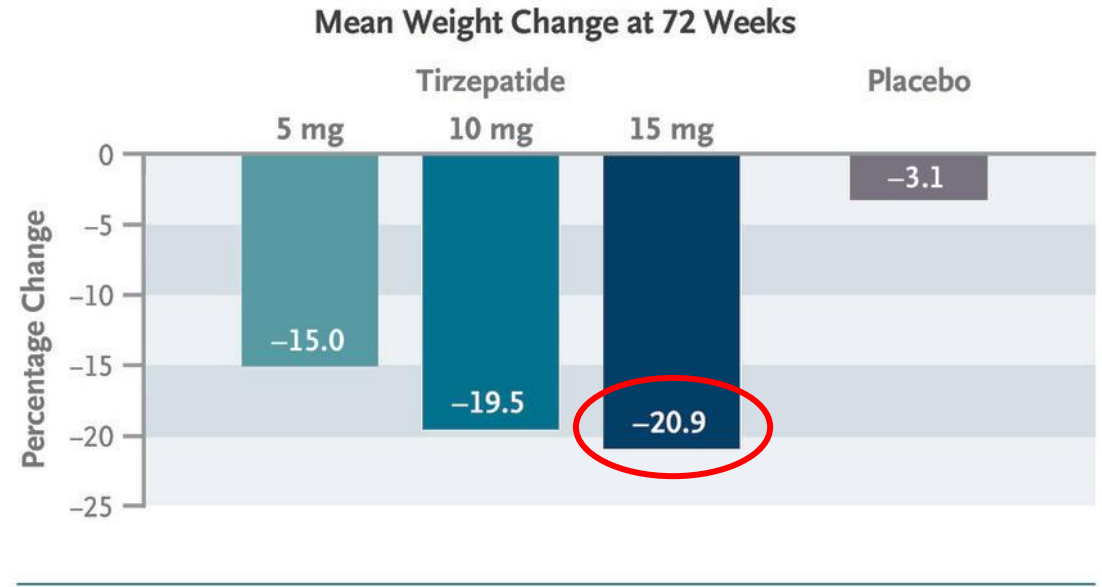
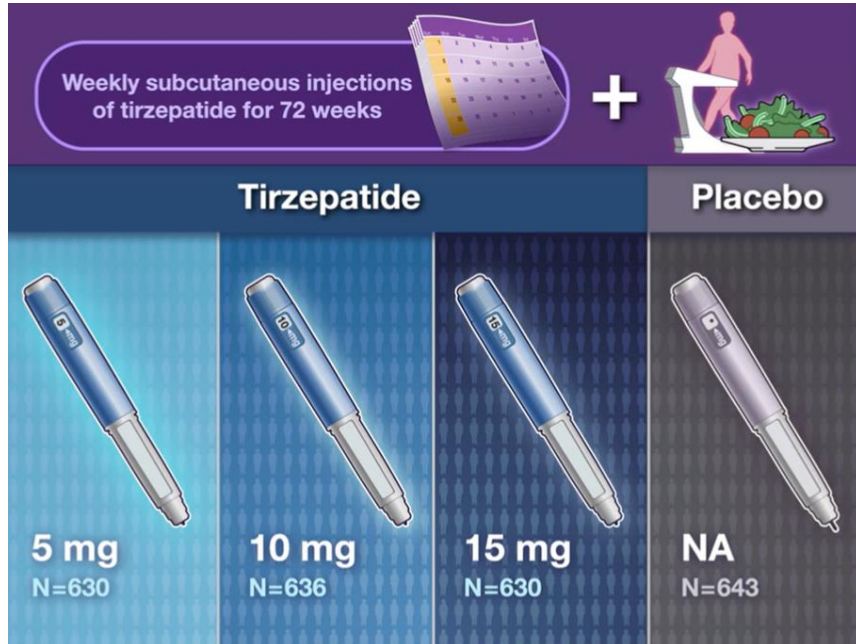


● Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

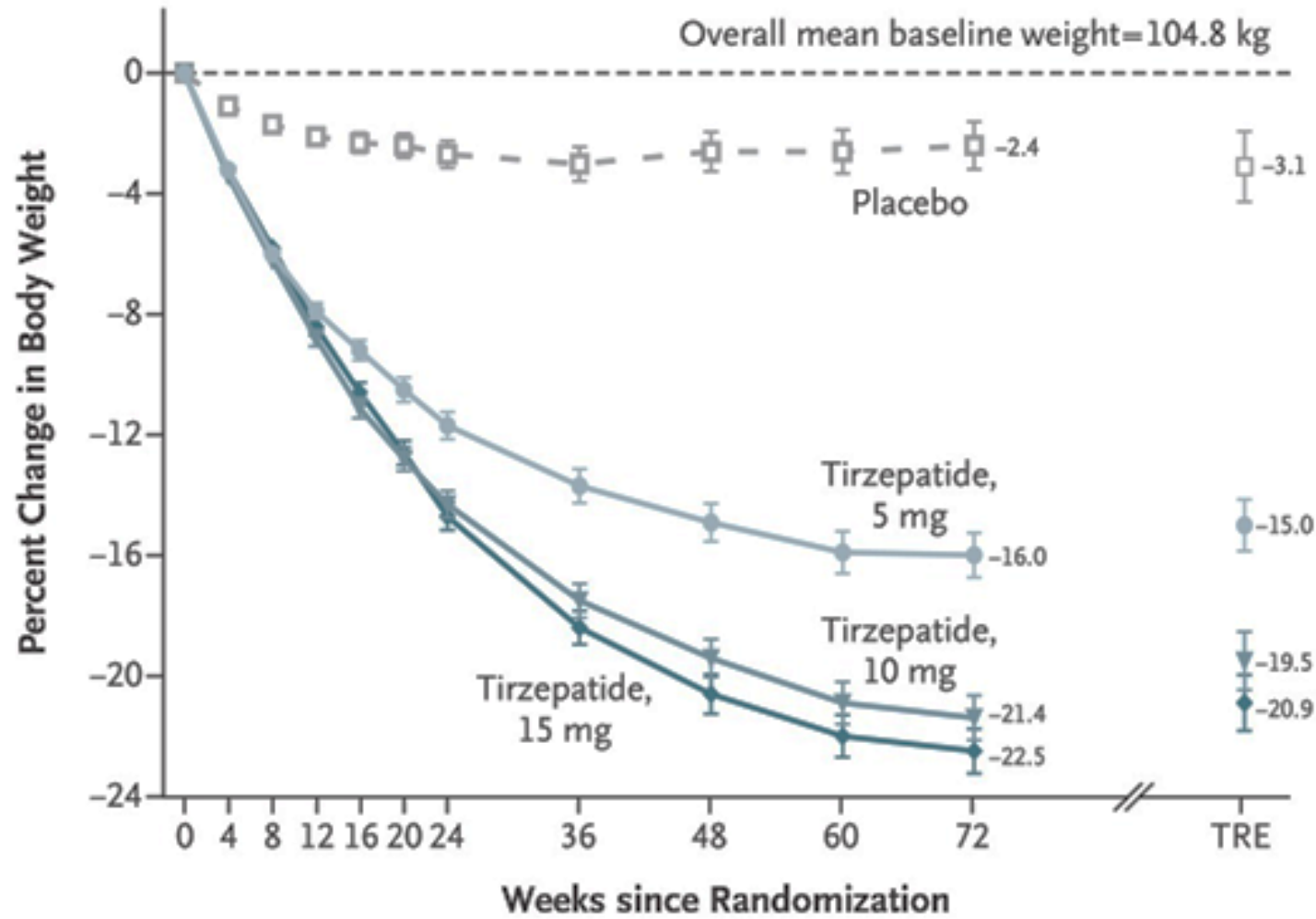
● Glucagon-like Peptide 1 Receptor Agonism

● Indirect Action

Tirzepatide

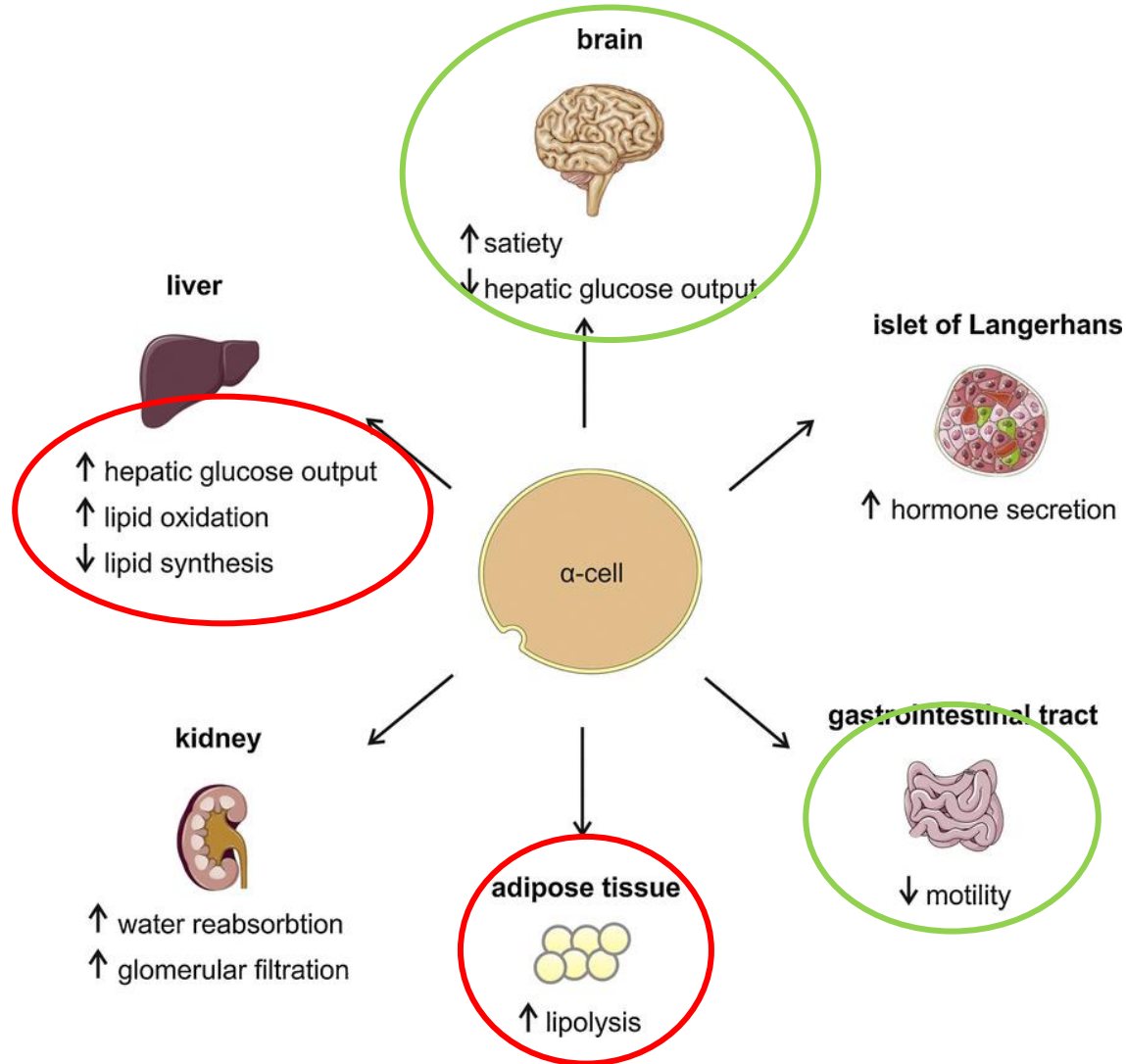


B Percent Change in Body Weight by Week (efficacy estimand)



SURMOUNT-MMO
in 2027

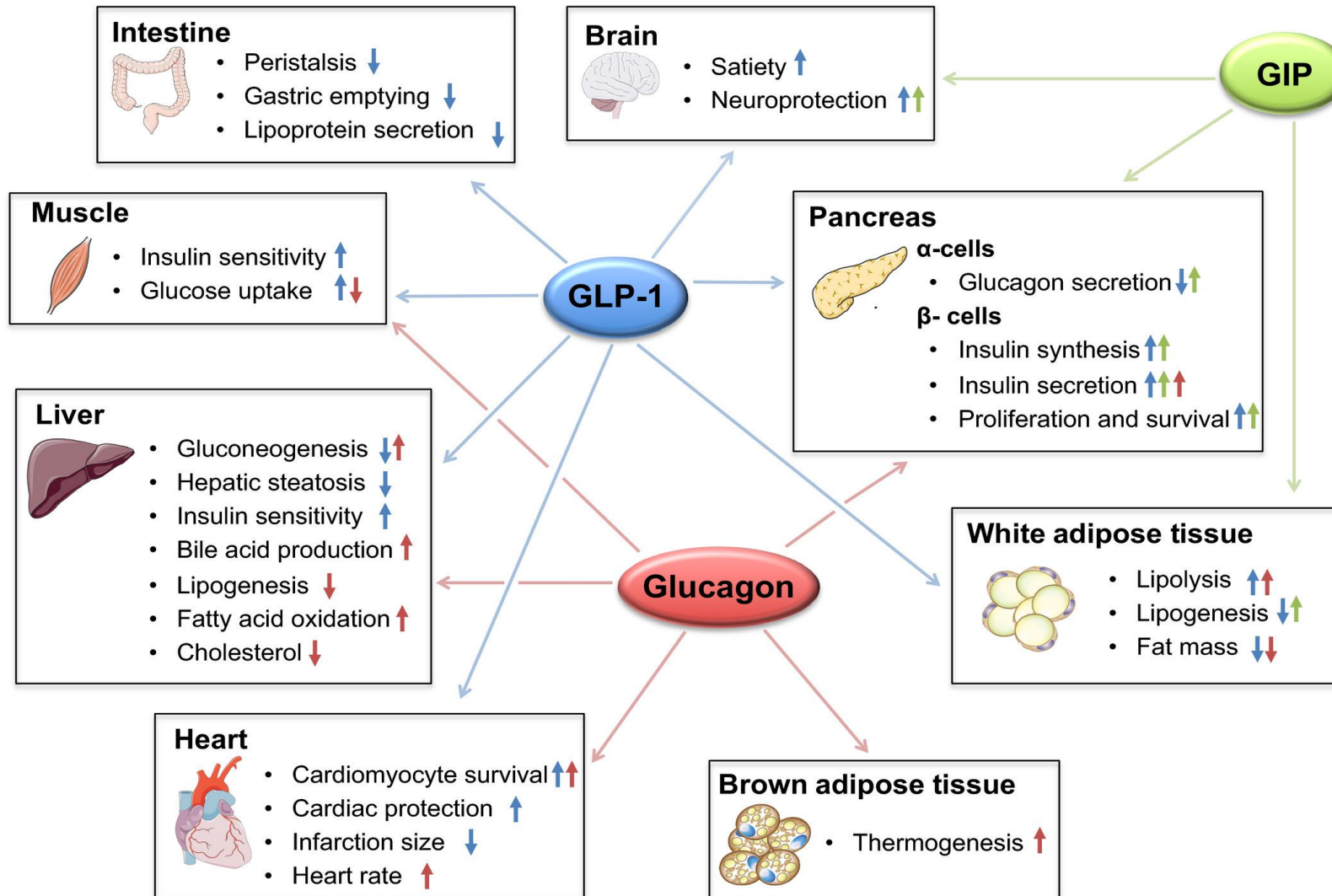
GLP1/glucagon dual agonist



GLP1/GcgR

- more than single mechanism in **BW reduction** (appetite suppression, thermogenesis and lipolysis)
- minimized risk of glucagon induce hyperglycemia
- reduce liver lipogenesis, inflammation, and fibrosis, with improved liver mitochondrial function

Poly-agonist



GLP-1 receptor agonists approved for obesity treatment		
Semaglutide	Weekly SC	STEP trials
Liraglutide	Daily SC	SCALE trials

MONOTHERAPY →

ENDO-PANCREATIC receptor agonists				
Cagrilintide	AMY RA	Phase II	Novo Nordisk	NCT03856047
ZP8396	AMY RA	Phase I	Zealand Pharma	NCT05096598
Amylin agonist LA	AMY RA	Phase I	Eli Lilly	Not available
DACRA QW II	AMY/CAL RA	Phase I	Eli Lilly	Not available

ORAL MONOTHERAPY →

ORAL GLP-1 receptor agonists				
Semaglutide	GLP-1 RA	Phase III	Novo Nordisk	NCT05035095
Danuglipron	sm GLP-1 RA	Phase II	Pfizer	NCT04707313
LY3502970	GLP-1R NPA	Phase II	Eli Lilly	NCT05051579

DUAL RA combinations →

ENTERO-ENDOCRINE receptor agonists/antagonists				
Tirzepatide	GIP/GLP-1 dual RA	Phase III	Eli Lilly	NCT04184622
CT388	GIP/GLP-1 dual RA	Phase I	Carmot Therapeutics	NCT04838405
Dapigliptide	GIP/GLP-2 dual RA	Phase I	Zealand Pharma	NCT04838405
AMG133	GIP Receptor Antagonist/GLP-1 RA	Phase I	Amgen	NCT04478708

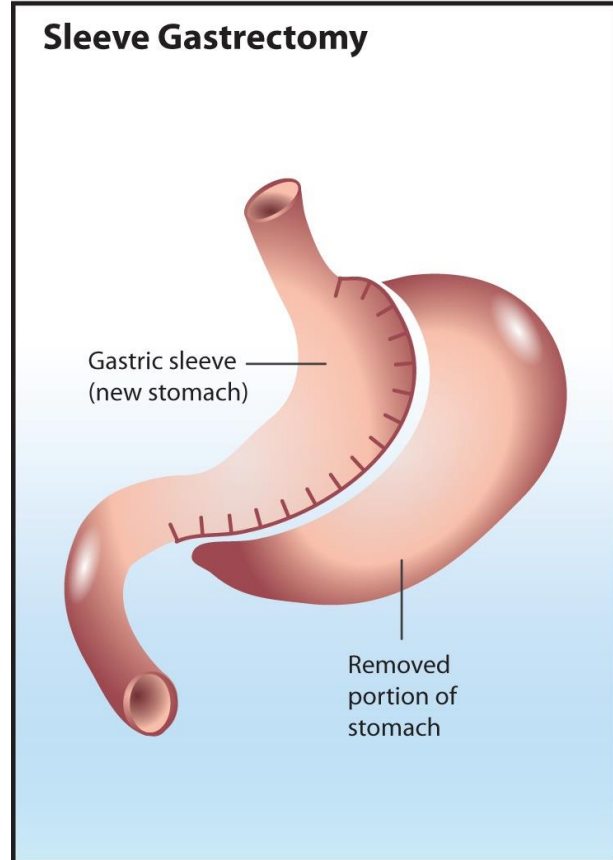
DUAL RA combinations →

PANCREATIC-ENTERO-ENDOCRINE receptor agonists				
Cagri-Sema	AMY/GLP-1 dual RA	Phase III	Novo Nordisk	NCT03600480
Pemvidutide	GCG/GLP-1 dual RA	Phase II	Altimune	NCT05295875
BI456906	GCG/GLP-1 dual RA	Phase II	Boehringer Ingelheim	NCT04667377
NN9277	GCG/GLP-1 dual RA	Phase I	Novo Nordisk	NCT03308721

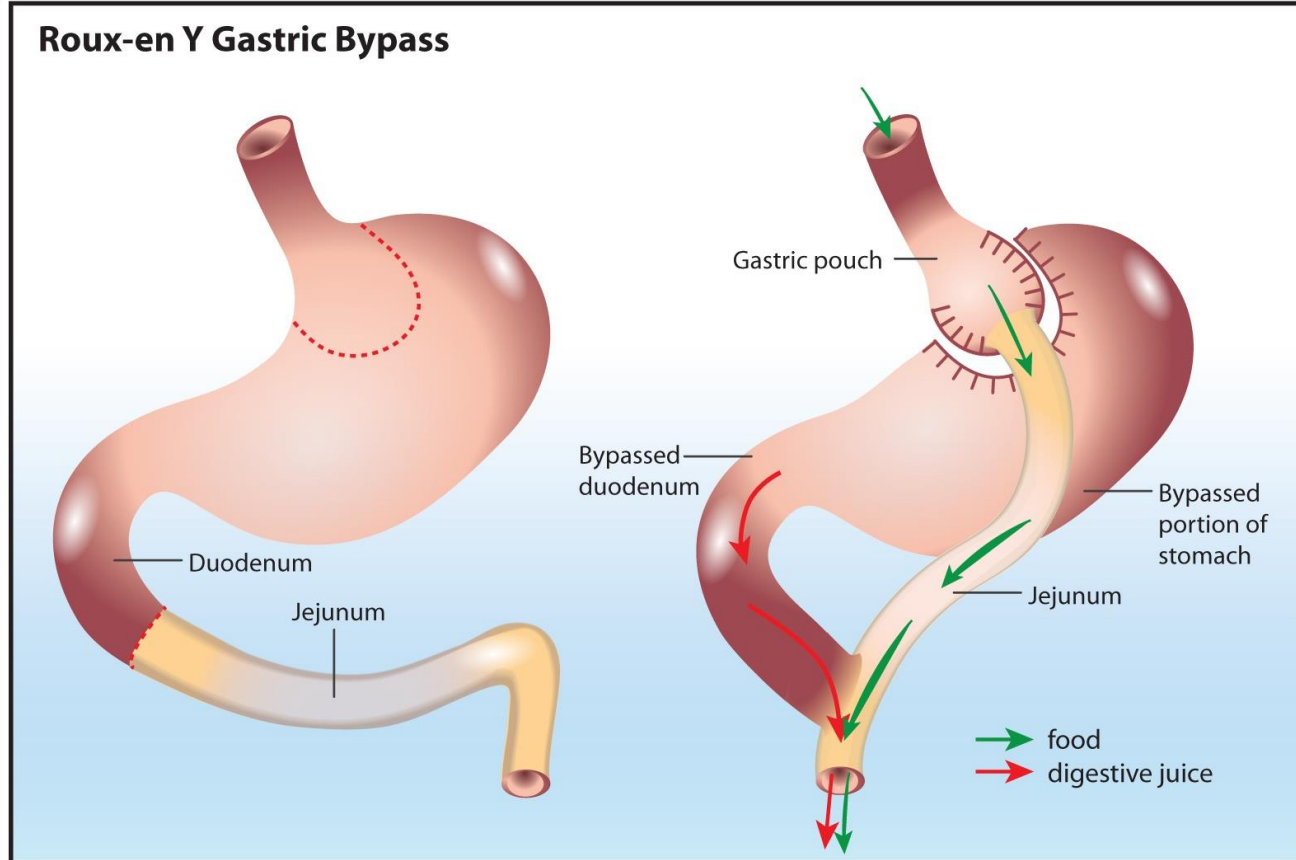
TRIPLE RA combinations →

PANCREATIC-ENTERO-ENDOCRINE receptor				
Retatrutide	GIP/GCG/GLP-1 triple RA	Phase II	Eli Lilly	NCT04881760

Sleeve Gastrectomy



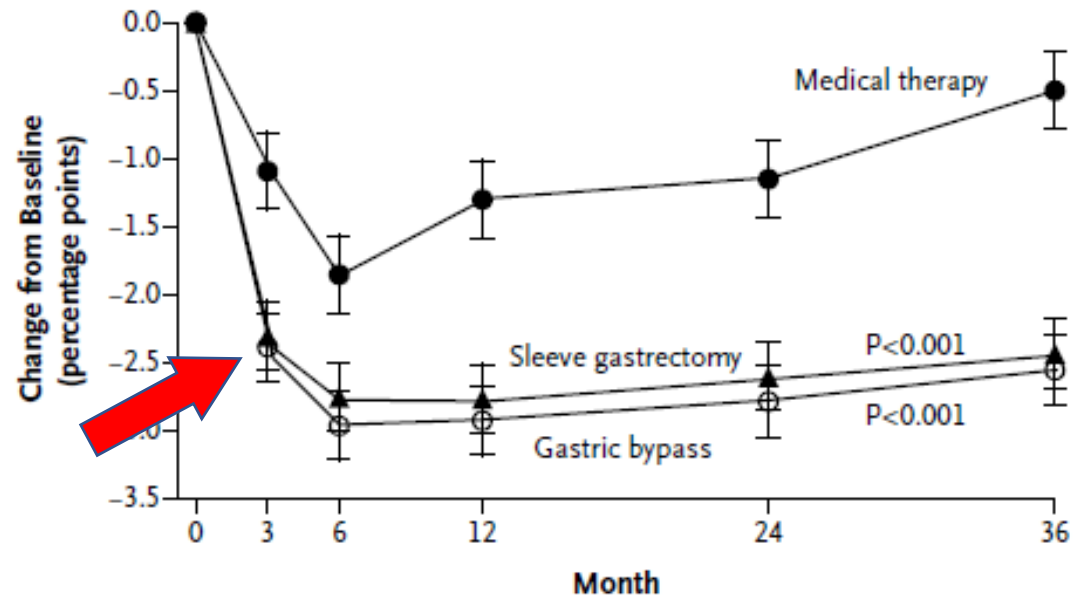
Roux en Y Gastric Bypass (RYGB)



Bariatric Surgery versus Intensive Medical Therapy for Diabetes

HbA1c

Glycated Hemoglobin

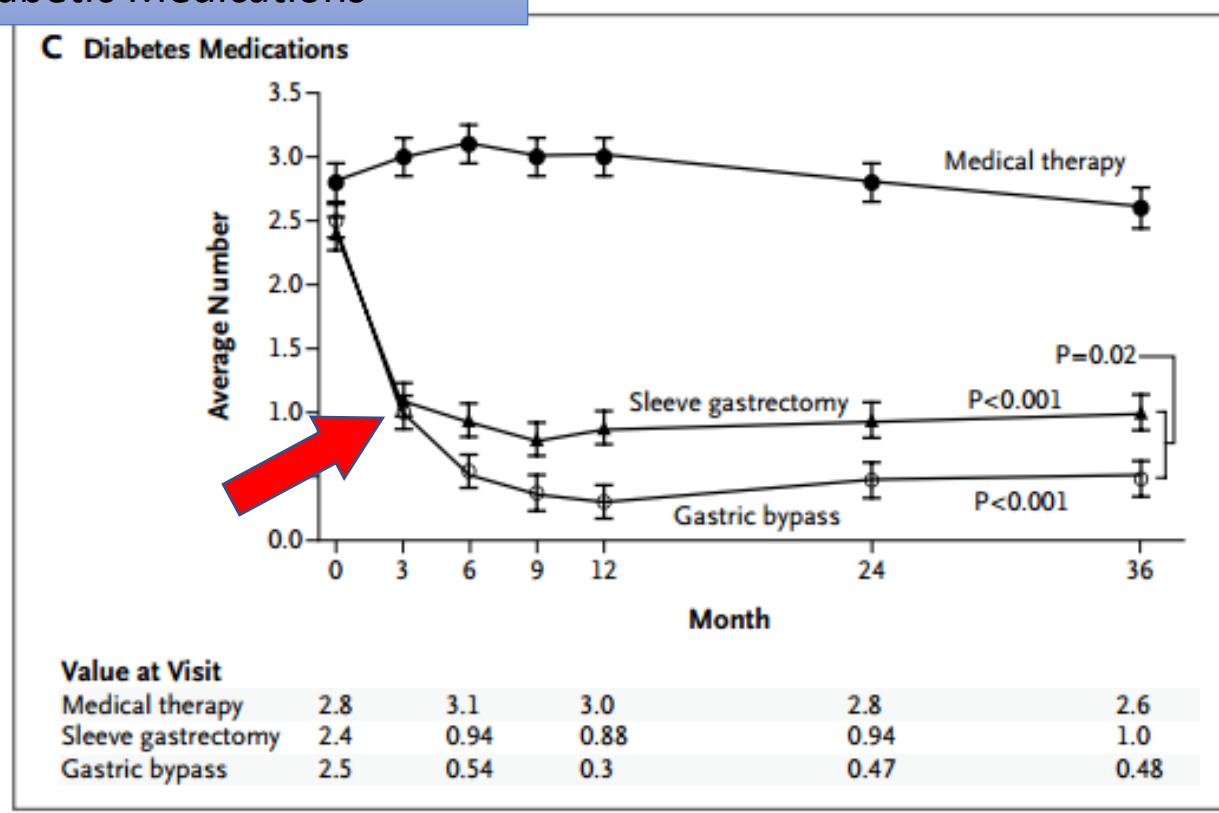


Value at Visit

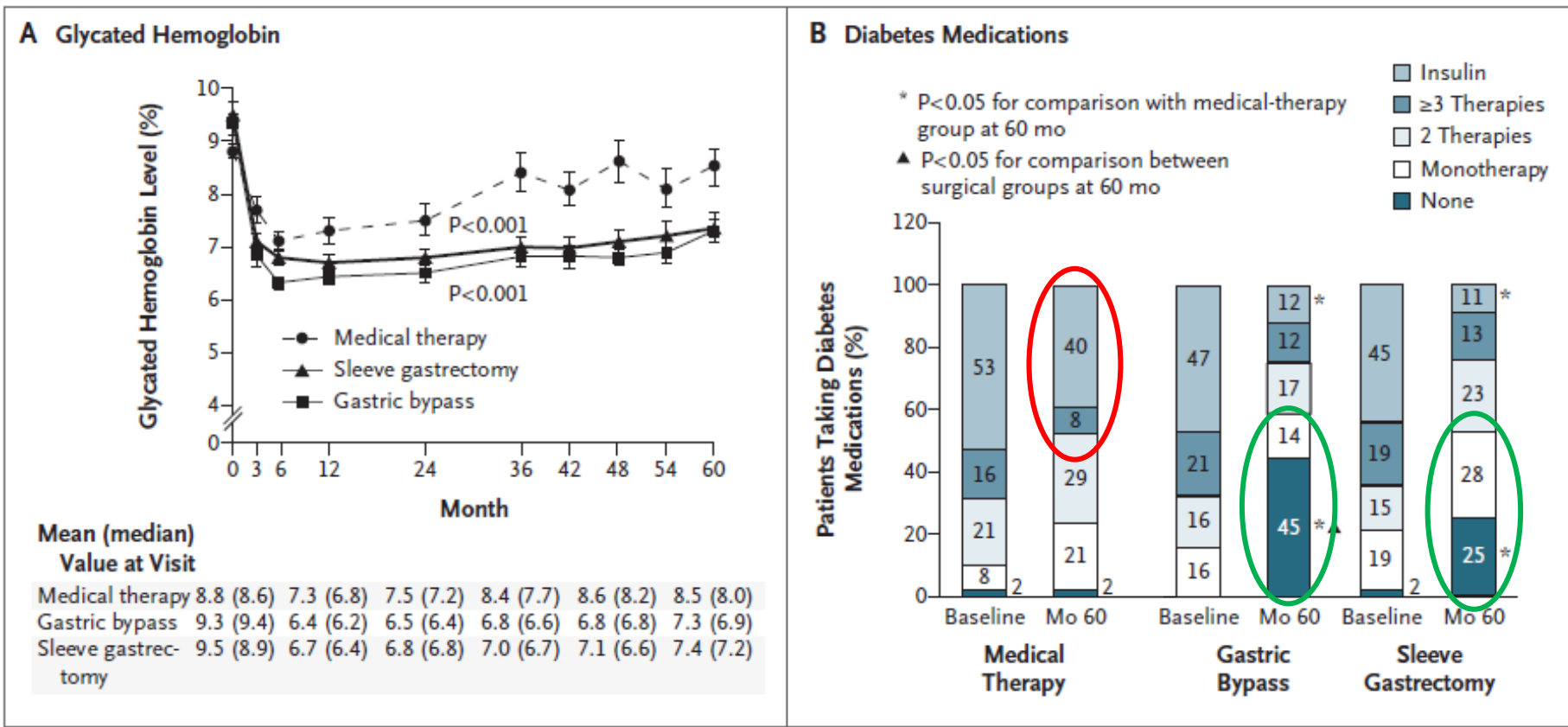
Medical therapy	9.0 (8.5)	7.1 (6.8)	7.5 (6.9)	7.7 (7.3)	8.4 (7.6)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.6 (6.4)	6.8 (6.8)	7.0 (6.6)
Gastric bypass	9.3 (9.2)	6.3 (6.2)	6.3 (6.1)	6.5 (6.4)	6.7 (6.6)

Bariatric Surgery versus Intensive Medical Therapy for Diabetes

Diabetic Medications



5-year outcomes



Long term

- Microvascular
- Macrovascular
- Death

Volume 44, Issue 1
January 2021



EMERGING THERAPIES: DRUGS AND REGIMENS | NOVEMBER 10 2020

The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study **FREE**







Pushpa Singh ; Nicola Adderley ; Anuradhaa Subramanian ; Krishna Gokhale; Rishi Singhal; Konstantinos A. Toulis; Srikanth Bellary ; Krishnarajah Nirantharakumar  ; Abd A. Tahrani

 Check for updates

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Diabetes Care 2021;44(1):116–124

<https://doi.org/10.2337/dc20-0571> [Article history](#) 

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Original Investigation

October 16, 2018

Association Between Bariatric Surgery and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe Obesity

David P. Fisher, MD¹; Eric Johnson, MS²; Sebastien Haneuse, PhD³; [et al](#)

[» Author Affiliations](#) | [Article Information](#)


JAMA. 2018;320(15):1570–1582. doi:10.1001/jama.2018.14619

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[Vol. 143, No. 15](#) > [Bariatric Surgery and Cardiovascular Outcomes in Patients With Obesity and Cardiovascular Disease:](#)


Bariatric Surgery and Cardiovascular Outcomes in Patients With Obesity and Cardiovascular Disease:

A Population-Based Retrospective Cohort Study

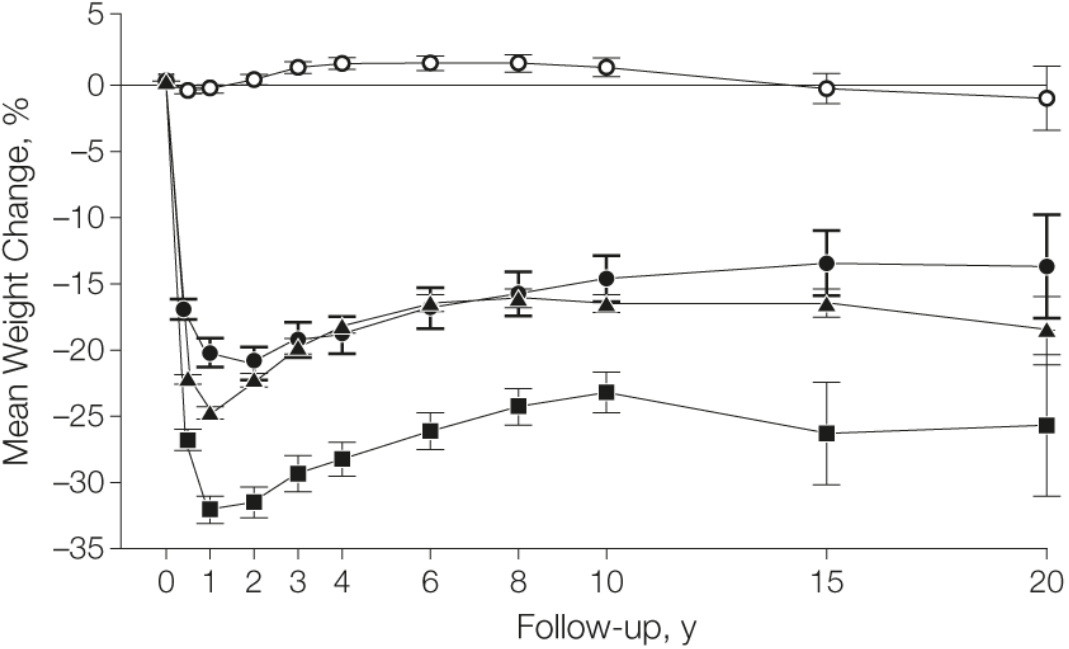
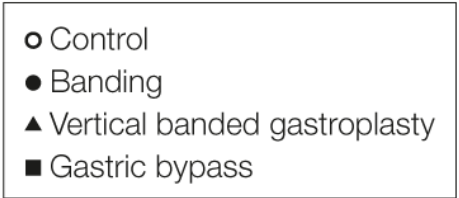
Aristithes G. Doumouras, Jorge A. Wong, J. Michael Paterson, Yung Lee, Branavan Sivapathasundaram, Jean-Eric Tarride, Lehana Thabane, Dennis Hong, Salim Yusuf and Mehran Anvari 

Originally published 5 Apr 2021 | <https://doi.org/10.1161/CIRCULATIONAHA.120.052386> | *Circulation*. 2021;143:1468–1480

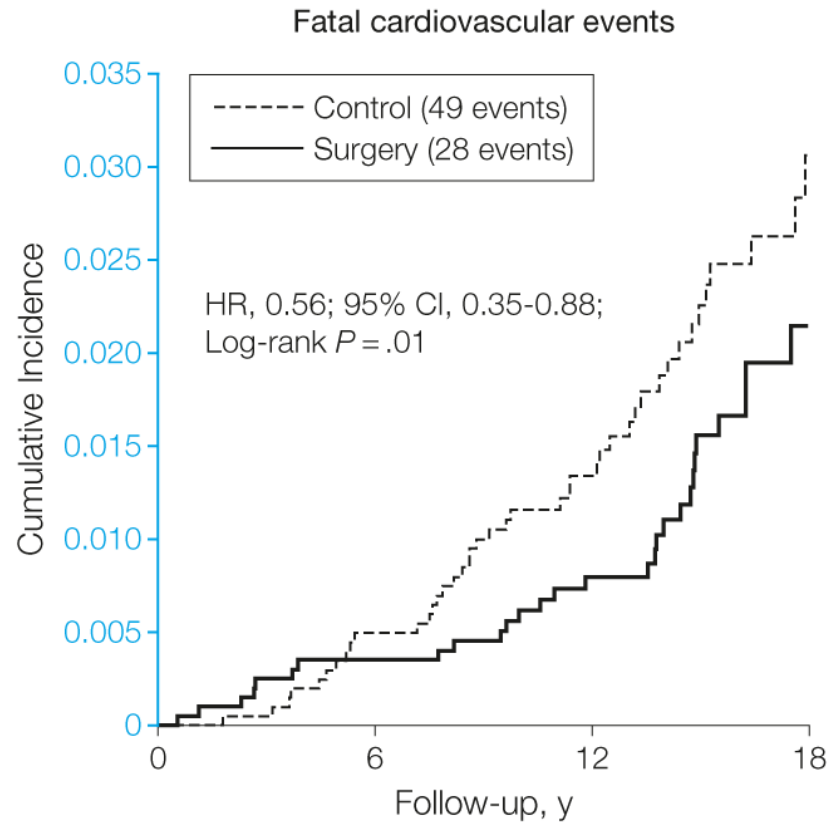
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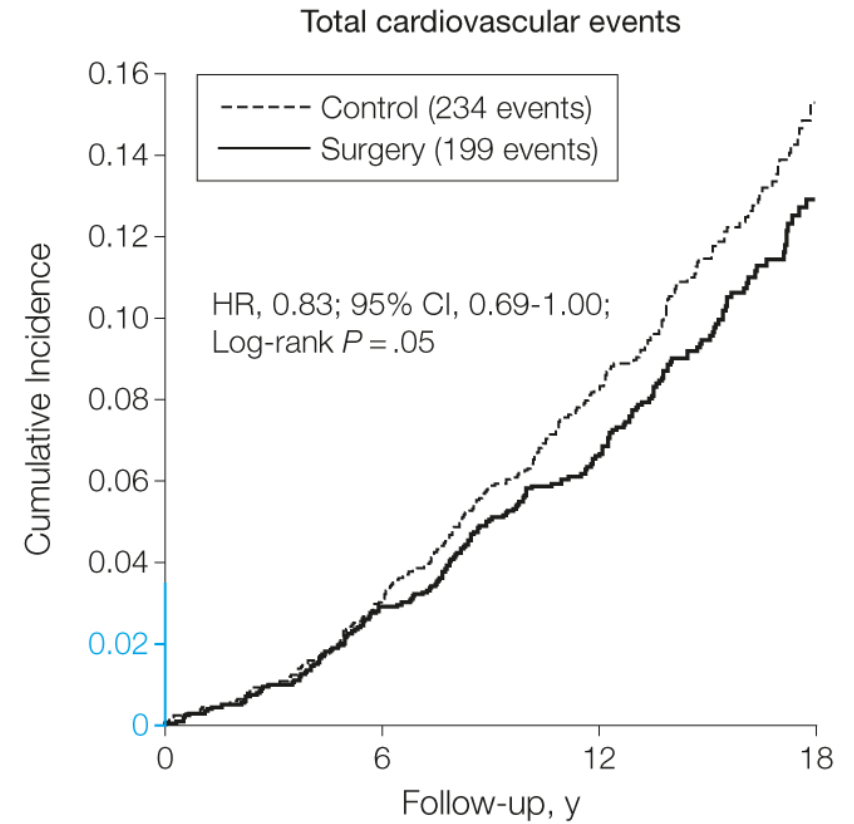
The Swedish Obese Subjects (SOS) study



No. of patients	0	1	2	3	15	20
Control	2037	1490	1242	1267	556	176
Banding	376	333	284	284	150	50
Vertical banded gastroplasty	1369	1086	987	1007	489	82
Gastric bypass	265	209	184	180	37	13



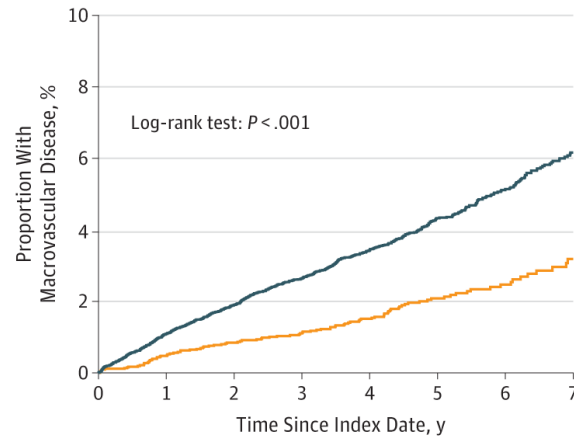
No. at risk				
Control	2037	1993	1423	405
Surgery	2010	1970	1557	412



No. at risk				
Control	2037	1945	1326	361
Surgery	2010	1921	1468	375

Association Between Bariatric Surgery and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe Obesity

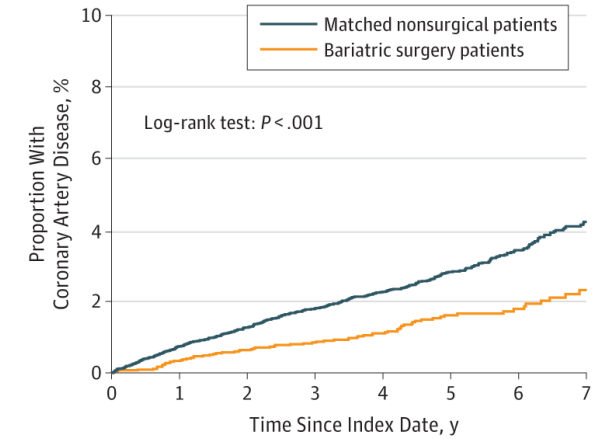
A All macrovascular disease events



Patients at risk

Matched nonsurgical patients	14934	13348	12053	11057	9438	5863	3677	2216
Bariatric surgery patients	5301	4784	4374	4046	3488	2238	1400	822

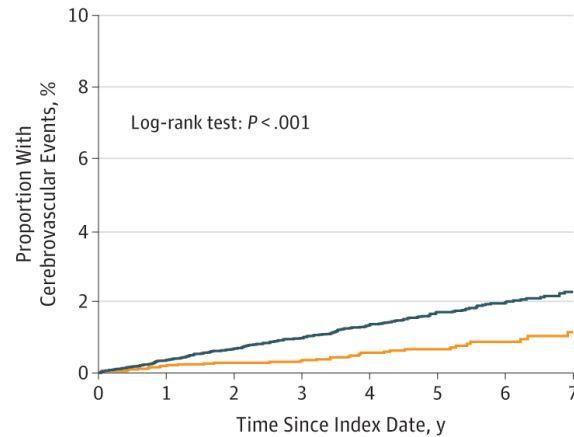
B Coronary artery disease events



Patients at risk

Matched nonsurgical patients	14934	13388	12116	11130	9523	5933	3732	2248
Bariatric surgery patients	5301	4790	4381	4054	3501	2245	1410	828

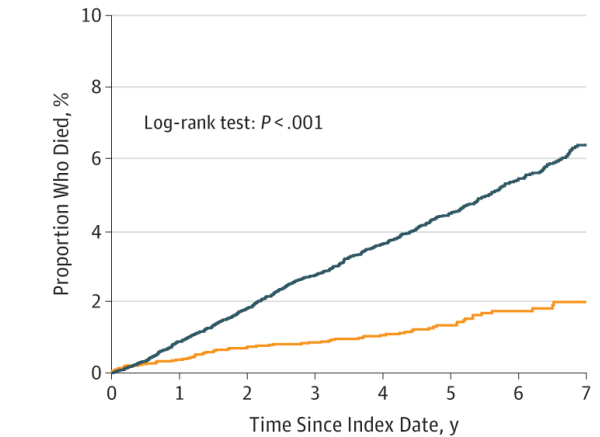
C Cerebrovascular events



Patients at risk

Matched nonsurgical patients	14934	13436	12190	11225	9614	6019	3797	2301
Bariatric surgery patients	5301	4796	4395	4072	3517	2267	1420	839

D All-cause mortality



Patients at risk

Matched nonsurgical patients	14934	13476	12257	11310	9712	6099	3860	2342
Bariatric surgery patients	5301	4804	4404	4082	3535	2278	1434	848

