Beyond Weight Loss: Obesity Management for Cardiovascular Disease Prevention

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Disclosure

Consultant: Amgen; Arrowhead Pharmaceutical; Astra Zeneca; Boehringer Ingelheim; Edwards Lifesciences; Eli Lilly; Esperion; Ionis Pharmaceuticals; Medtronic; Merck; New Amsterdam; Novartis; Novo Nordisk; Pfizer

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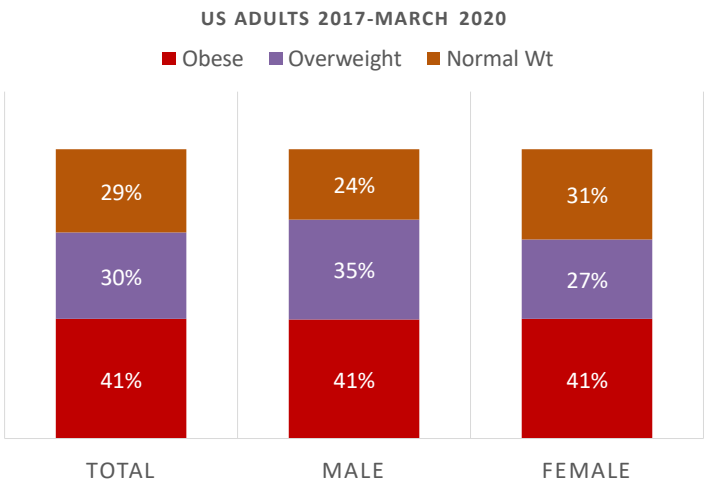
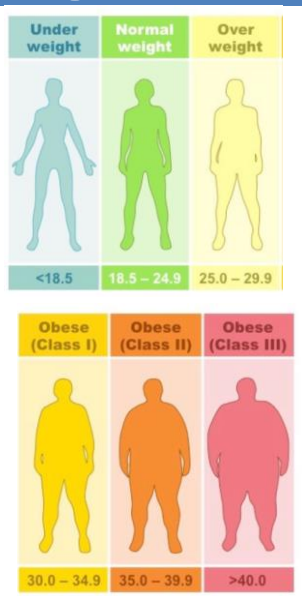
Learning Objectives

1. Review the cardiovascular risks associated with obesity
2. Summarize the benefits and challenges associated with lifestyle, bariatric, and pharmacologic interventions in the treatment of obesity for cardiovascular risk reduction.
3. Review the published and on-going cardiovascular outcome trials evaluating the cardiovascular benefits of glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapies in patients with or at high risk of cardiovascular disease or heart failure

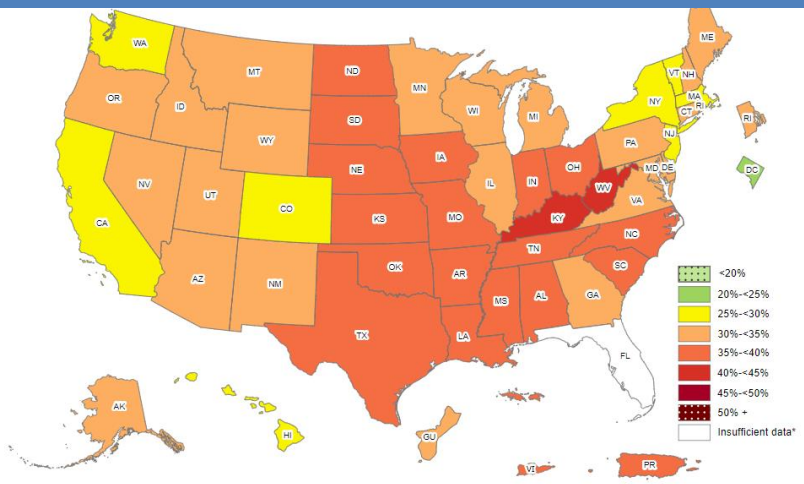
Obesity Is a Major Health Problem. 71% of US Adults Are Overweight or Obese





Tsao CW... **Michos ED**... Martin SS. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association, Circulation. 2023

Prevalence of Obesity in US in 2021 by State



•All states and territories had more than 20% of adults with obesity.

Source: Behavioral Risk Factor Surveillance System
https://www.cdc.gov/obesity/data/prevalence-maps.html

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More Than Half the Global Population Estimated to Be Overweight/Obese by 2035

Table 1.1: Global overweight and obesity 2020–2035

Numbers of people (aged over 5 years) and percentage of the population with overweight or obesity*

	2020	2025	2030	2035
Number with overweight or obesity (BMI≥25kg/m²) (millions)	2,603	3,041	3,507	4,005
Number with obesity (BMI ≥30kg/m²) (millions)	988	1,249	1,556	1,914
Proportion of the population with overweight or obesity (BMI ≥25kg/m²)	38%	42%	46%	51%
Proportion of the population with obesity (BMI ≥30kg/m²)	14%	17%	20%	24%

** For children and adolescents, overweight and obesity are defined using the WHO classification of +1SD and +2SD above median growth reference.*

World Obesity Federation. World Obesity Atlas 2023

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~1 in 4 Adults Globally to Have Obesity by 2035. Economic Impact 4.3 Trillion.

Adults (aged 20 years and over)

	Men 2020	Men 2025	Men 2030	Men 2035
Number with obesity (millions)	347	439	553	690
Proportion of all men	14%	16%	19%	23%
	Women 2020	**Women 2025**	**Women 2030**	**Women 2035**
Number with obesity (millions)	466	568	693	842

Table 1.3: Global economic impact of high BMI (BMI ≥25kg/m²) 2020–2035

	2020	2025	2030	2035
Economic impact (US$ at 2019 value) (trillions)	US$ 1.96	US$ 2.47	US$ 3.23	US$ 4.32
Impact as proportion of total global GDP	2.4%	2.5%	2.7%	2.9%

World Obesity Federation. World Obesity Atlas 2023

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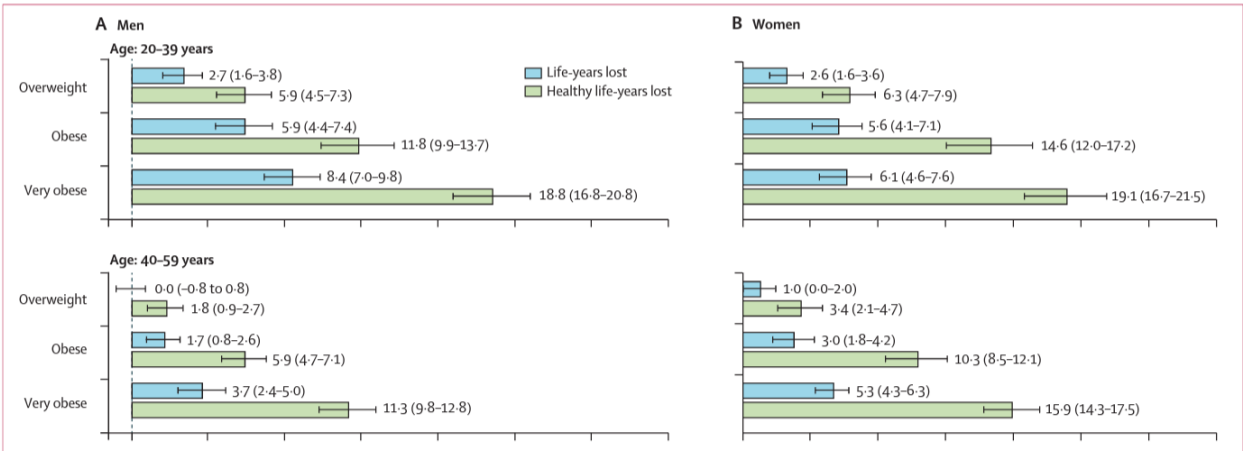
Obesity Increases Loss of Life-Years and the Quality of Life



Calculated years of life lost and healthy life-years lost in men (A) and women (B) compared with those with an ideal bodyweight. Bodyweight categories are ideal (BMI 18·5 to <25 kg/m²), overweight (25 to <30 kg/m²), obese (30 to <35 kg/m²), or very obese (≥35 kg/m²). Data are based on cardiometabolic risk factors in US adults in the National Health Examinations and Nutrition Survey data from 2003–10.25 Error bars show the 95% CI for each estimate.

Grover SA et al. Lancet Diabetes Endocrinol 2015; 3: 114–22

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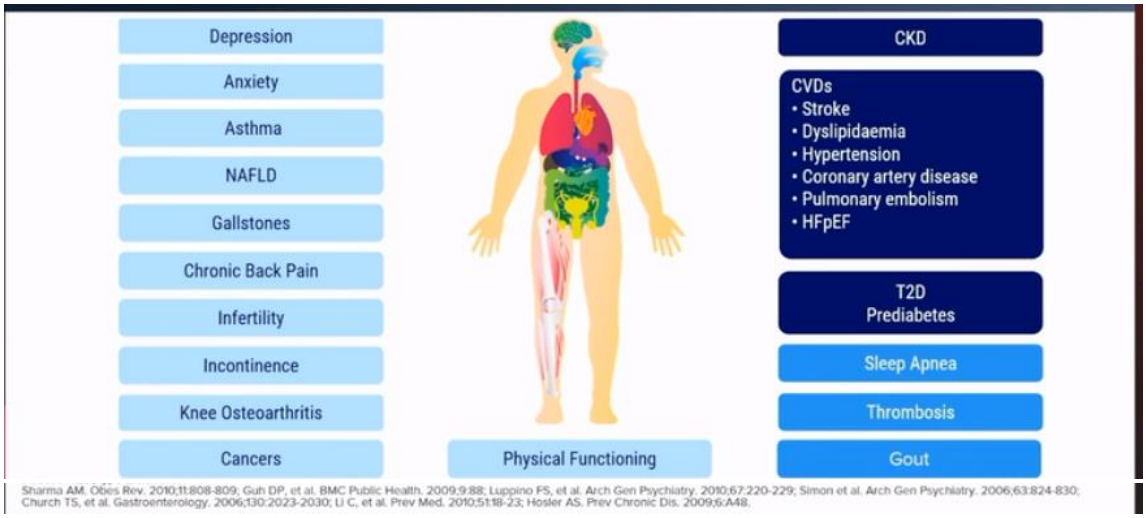
Obesity Is the Signal Disease for Multiple Comorbidities



Sharma AM. Obes Rev. 2010;11:808-809; Guh DP, et al. BMC Public Health. 2009;9:88; Luppino FS, et al. Arch Gen Psychiatry. 2010;67:220-229; Simon et al. Arch Gen Psychiatry. 2006;63:824-830; Church TS, et al. Gastroenterology. 2006;130:2023-2030; Li C, et al. Prev Med. 2010;51:18-23; Hosler AS. Prev Chronic Dis. 2009;6:A48.

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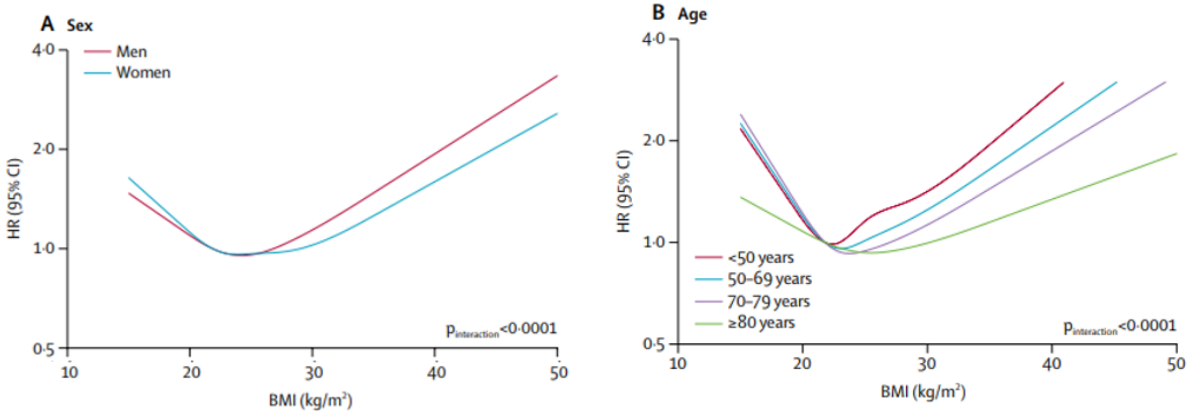
BMI and All Cause Mortality Among Never Smokers [3.6 Million Adults in the UK]

Compared to 20 kg/m2, estimated hazard ratio per 5 kg/m^2 increase in BMI was 0.81 (95% CI 0.80-0.82) below 25 kg/m^2 (nadir 21-25 kg/m2) and 1.21 (1.20-1.22) above this point.



Bhaskaran K et al. Lancet Diabetes Endocrinol 2018; 6: 944–53

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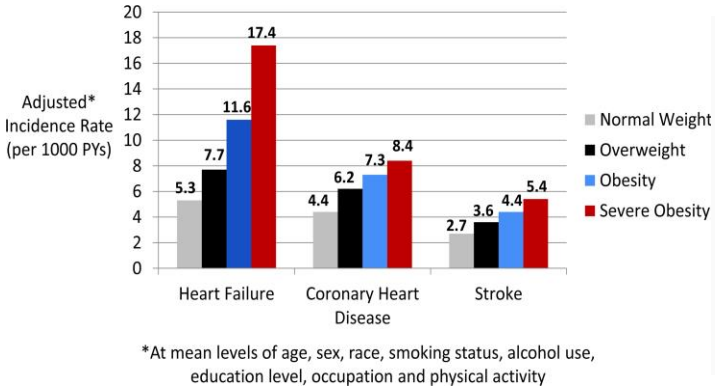
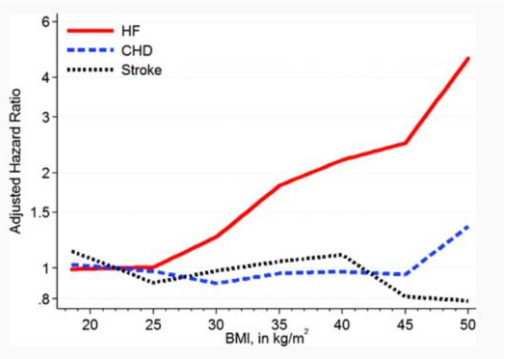
Obesity and Subtypes of Incident Cardiovascular Disease

Obesity – stronger risk factor for Heart Failure than for other types of CVDs



*At mean levels of age, sex, race, smoking status, alcohol use, education level, occupation and physical activity



Ndumele CE et al. J Am Heart Assoc. 2016;5:e00392

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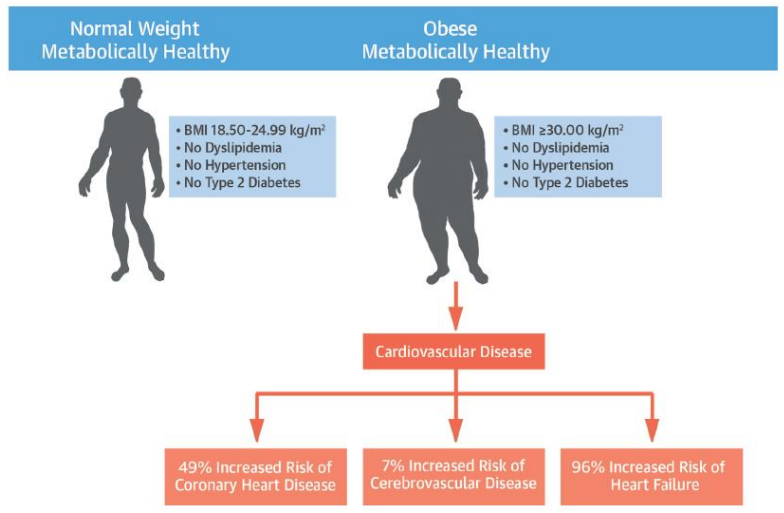
Even "Metabolically Healthy" Obesity Is Associated with Increased Risk of Future CVD



Caleyachetty, R. et al. J Am Coll Cardiol. 2017;70(12):1429-37.

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BMI-years and Incident HF (MESA)
Duration of Elevated BMI Independent Risk Factor

- Participant mean±SD age at the baseline examination was 62.2±10.2 years.
- Self reported weights at age 20 and 40 were asked
- Follow-up for incident HF, median follow-up 13 years

More years at higher BMI associated with HF risk even after adjusting for current BMI

Table 3. Incidence Rates and Adjusted Hazard Ratios (95% CI) for Incident Heart Failure Associated With BMI at Each Age Point

	N Events/Person-Year	IR (95% CI)*	Model 1†	Model 2‡	Model 3§
BMI at age 20 y, per 5 kg/m^2 higher‖	290/74 317	4.3 (3.8, 4.7)	1.44 (1.24, 1.67)¶	1.40 (1.20, 1.63)¶	1.27 (1.07, 1.50)¶
BMI at age 40 y, per 5 kg/m^2 higher‖	290/74 317	4.3 (3.8, 4.7)	1.53 (1.39, 1.70)¶	1.45 (1.29, 1.62)¶	1.36 (1.18, 1.57)¶
BMI at baseline, per 5 kg/m^2 higher	290/74 317	4.3 (3.8, 4.7)	1.43 (1.28, 1.60)¶	1.31 (1.16, 1.48)¶	
Time-varying BMI (v1–v5) per 5 kg/m^2 higher	284/73 643	3.9 (3.4, 4.3)	1.45 (1.30, 1.62)¶	1.34 (1.19, 1.51)¶	

*IR: (95% CI) per 1000 person-y, adjusted for age, sex, race, and center.
† Model 1 (demographics and SES model): adjusted for age at baseline, sex, race/ethnicity, center, and education.
‡ Model 2 (+CVD risk factors): additionally adjusted for smoking, physical activity, healthy diet score, total cholesterol, HDL-C, use of cholesterol-lowering medications, systolic blood pressure, use of antihypertensive medications, and diabetes mellitus.
§ Model 3 (for analyses of BMIs at age 20 and 40 y): additionally adjusted for BMI at MESA baseline

Self-reported lifetime weight is a low-tech tool easily utilized in any clinical encounter. Although subject to recall bias, self-reported weights may provide prognostic information about future HF risk, incremental to current BMI, in a multiethnic cohort of middle-aged to older adults.

Fliotsos M…..**Michos ED**. Body Mass Index From Early-, Mid-, and Older-Adulthood and Risk of Heart Failure and Atherosclerotic Cardiovascular Disease: MESA, J Am Heart Assoc 2018; 7 (22): e009599

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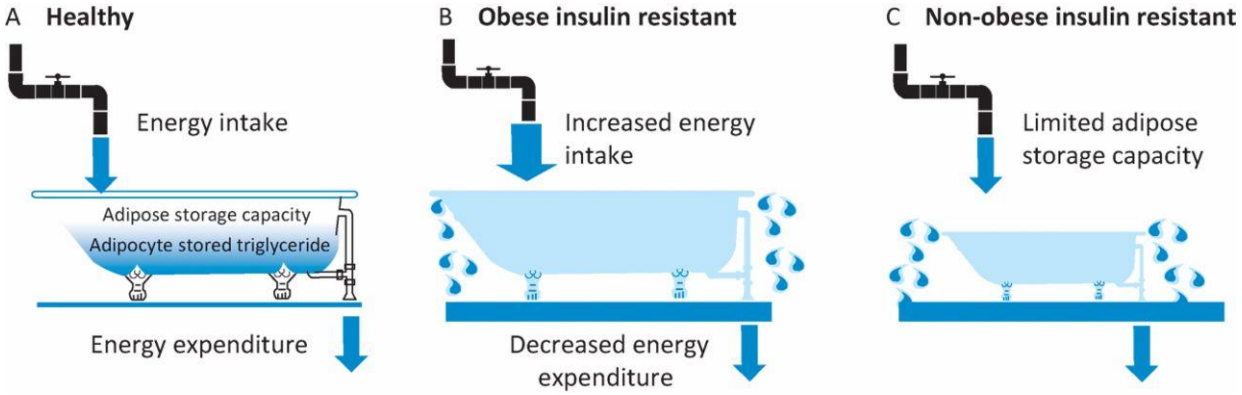
The 'Soggy Bathroom Carpet' Model of Over-nutrition-related Metabolic Disease



Stephen O'Rahilly. Clinical Medicine 2016 Vol 16, No 6: 551–64

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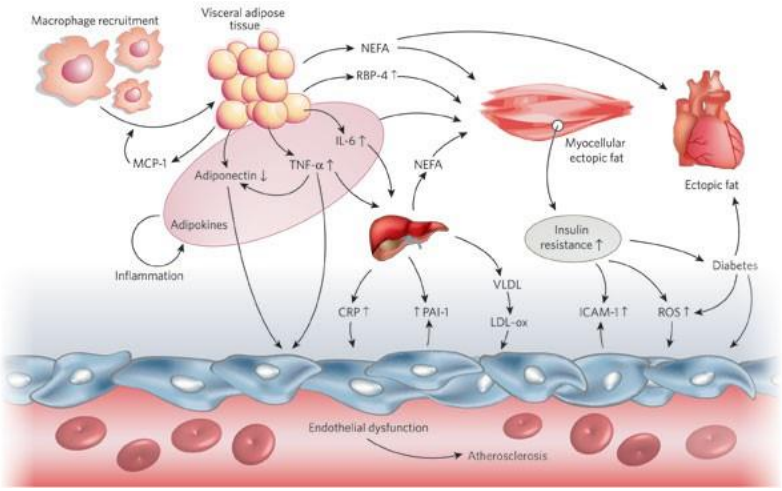
Adipose Tissue as an Active Endocrine and Paracrine Organ



- Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators, such as leptin, adiponectin, IL-6 and TNF-α, that influence not only body weight homeostasis but also insulin resistance, diabetes, lipid levels, coagulation, fibrinolysis, inflammation and atherosclerosis

Van Gaal L et al. *Nature*. 2006:444, 875–880. https://doi.org/10.1038/nature05487

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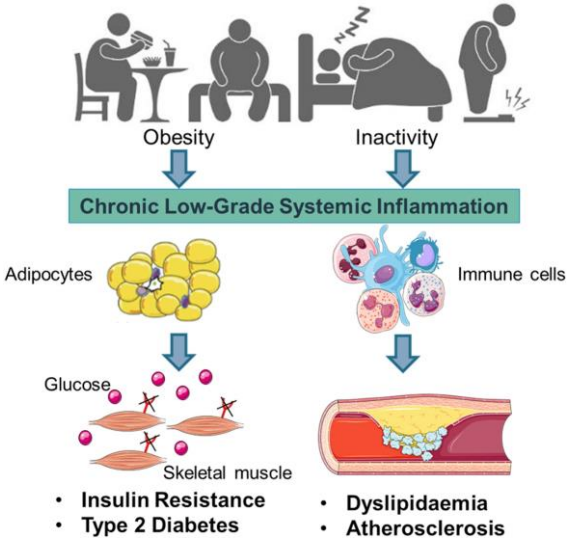
Obesity Contributes to a Chronic Low-grade Systemic Inflammation



Roche, H. *Proceedings of the Nutrition Society. 2019; 78*(3): 313-318

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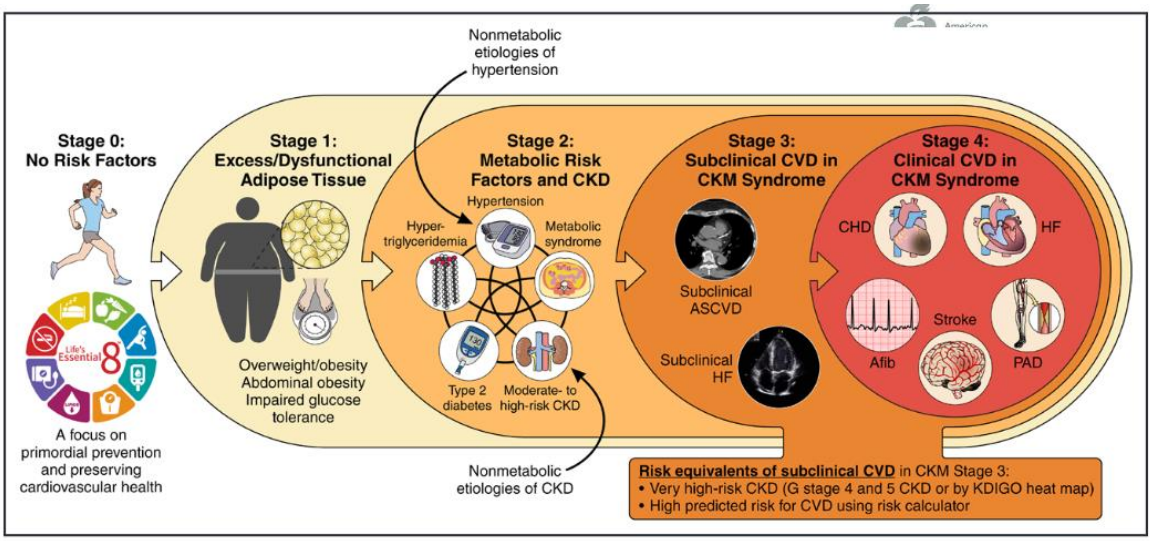
Stages of CKM Syndrome



Ndumele CE et al. Circulation. 2023;148:00–00. DOI: 10.1161/CIR.0000000000001184

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Guidelines Recommend Weight Loss as CV Prevention Strategy for Those Overweight/Obese

ACC/AHA Guideline

Recommendations for Adults with Overweight and Obesity		
COR	**LOE**	**Recommendations**
I	**B-R**	**In individuals with overweight and obesity, weight loss is recommended to improve the ASCVD risk factor profile.**

Arnett DK, Blumenthal RS,….**Michos ED**…et al. Circulation 2019

ESC Guideline

Recommendations	Class	Level
It is recommended that overweight and obese people aim for a reduction in weight to reduce BP, dyslipidaemia, and risk of type 2 DM, and thus improve their CVD risk profile.	I	A
While a range of diets are effective for weight loss, it is recommended that a healthy diet in regard to CVD risk is maintained over time.	I	A
Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.	IIa	B

Visseren FLJ et al. Eur Heart J. 2021;42(34):3227-3337.

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What Is Clinically Meaningful Weight Loss?

Measures of glycemia[1] Triglycerides[1]	-3%
Systolic and diastolic blood pressure Hepatic steatosis measured by MRS[2] Measures of feeling and function: Symptoms of urinary stress incontinence[3] Measures of sexual function[4,5] Quality of life measures(IWQOL)[6]	-5%
NASH Activity Score measured on biopsy[7] Apnea-hypopnea index[8]	-10%
Reduction in CV events, mortality, remission of T2DM	-15%

- 1. Wing et al. Diabetes Care 2011;34:81-1486. 2. Lazo et al. Diabetes Care 2010;33:2156–63.3. Phelan et al. Urol. 2012;187:939-44. 4. Wing et al. Diab Care 2013;36:2937-44. 5. Wing et al. Journal of Sexual Medicine 2010 ; 7:156-65. 6. Crosby, Manual for the IWQOL-LITE Measure. 7. Promrat et al. Hepatology 2010;51:121–29. 8. Foster et al. Arch Intern Med 2009;169:1619–26.

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In Look-Ahead, ≥10% Weight Loss Associated with Favorable CV Outcomes

	Weight-change categories (percentage weight loss in first year; n=4834)				
	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	p value
Primary outcome					
Events per person-years	289/17 075	141/7870	154/8570	128/8942	..
Crude rate per 100 person-years	1·69	1·79	1·80	1·43	..
Unadjusted hazard ratio (95% CI)	1·00	1·07 (0·88–1·31)	1·07 (0·88–1·31)	0·83 (0·67–1·02)	0·21
Adjusted hazard ratio†(95% CI)	1·00	1·08 (0·88–1·33)	1·16 (0·95–1·42	0·79 (0·64–0·98), p=0·034*	0·17

Primary outcome: composite of death from CV causes, non-fatal MI, non-fatal stroke, or admission to hospital for angina

Gregg EW et al. Lancet Diabetes Endocrinol. 2016 November ; 4(11): 913–921

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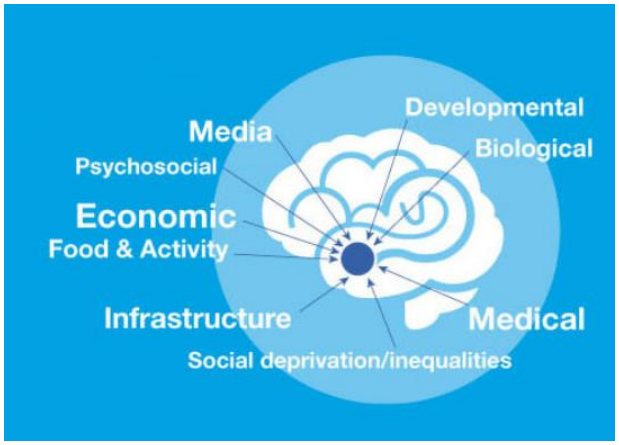
Obesity: A Serious but Treatable Chronic Disease



European Association for the Study of Obesity
https://easo.org/obesity-is-a-chronic-disease/

- Obesity is complex chronic disease influenced by genetic, hormonal, neural, environmental, & social factors

70%-80% of our BMI is determined by genes.*

- It's about CHEMISTRY not CHARACTER

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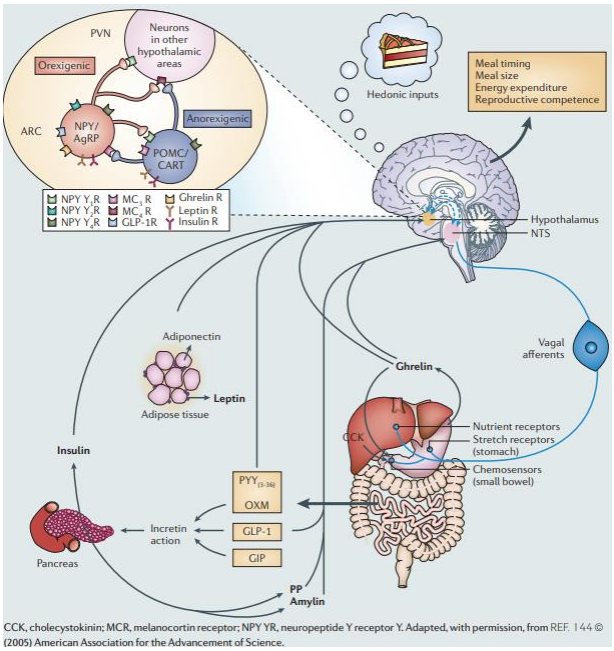

CCK, cholecystokinin; MCR, melanocortin receptor; NPY YR, neuropeptide Y receptor Y. Adapted, with permission, from REF. 144 © (2005) American Association for the Advancement of Science.

Cooke D, et al., Nat Rev Drug Discovery 2006; 5: 919-931.

Neural Basis of Weight Control

Obesity Is a Brain-related Disorder

- The hypothalamus plays an important role in the regulation of body weight by balancing the intake of food, energy expenditure, and body fat stores
- However its normal function can be disrupted by biological & environmental factors.
- Once disrupted, feelings of hunger and satiety can be affected

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Weight Regain Is Common

- Data from 14 studies assessing reduced-calorie diets demonstrated that although initial weight loss was achieved (−4.5 kg to −30 kg), most individuals regained a large proportion of their initial weight loss within a few years

European Association for the Study of Obesity
https://easo.org/obesity-is-a-chronic-disease/

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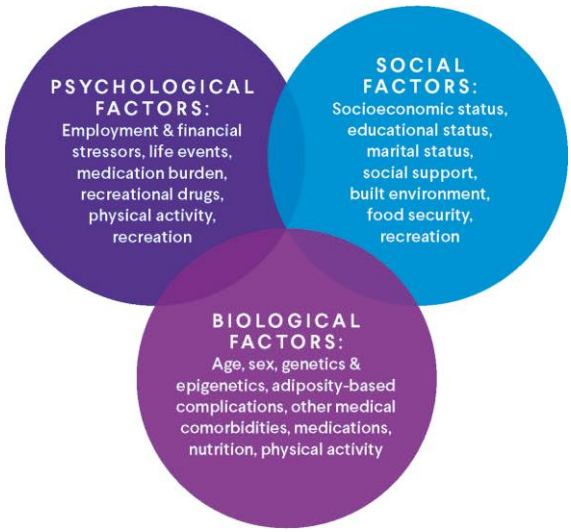
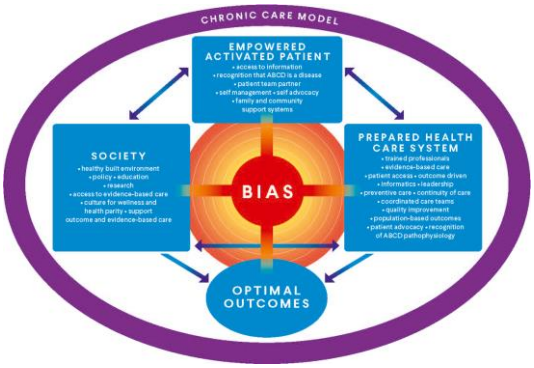
Biopsychosocial Model for Obesity/Adiposity-based Chronic Disease



Weight bias disrupts chronic care model



Nadolsky K et al. Endocrine Practice 2023 DOI: (10.1016/j.eprac.2023.03.272)

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5 A's for Obesity/Adiposity Based Chronic Disease (ABCD)

- **ASK** if you can discuss weight and the health impact of ABCD
- **ASSESS** health status and complications
- **ADVISE** on treatment options based on the severity of ABCD
- **AGREE** on treatment plan and weight-loss goals
- **ASSIST** in the continuous process of weight management with reassessment of goals and treatment options

Nadolsky K et al. Endocrine Practice 2023 DOI: (10.1016/j.eprac.2023.03.272)

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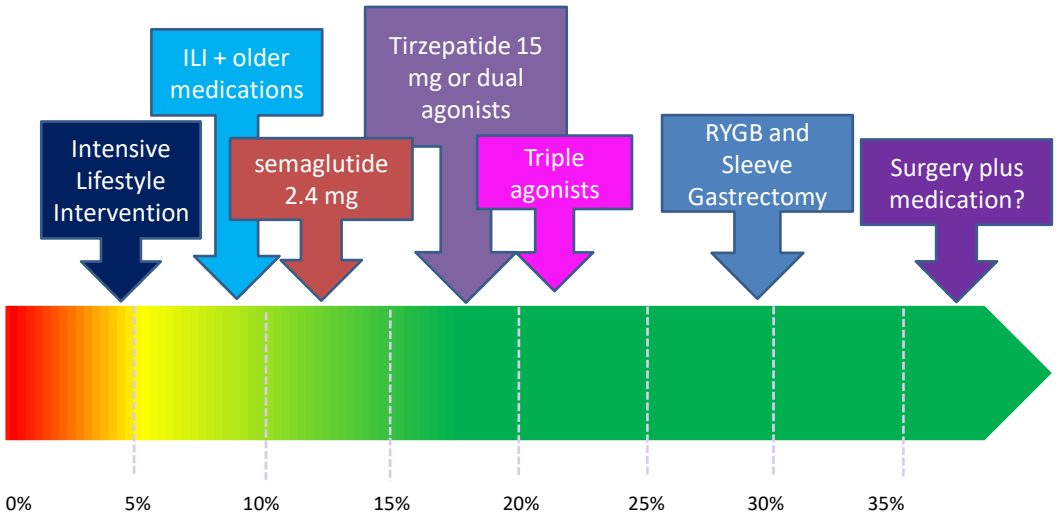
Tools for Achieving Clinically Meaningful Weight Loss



ILI; intensive lifestyle intervention

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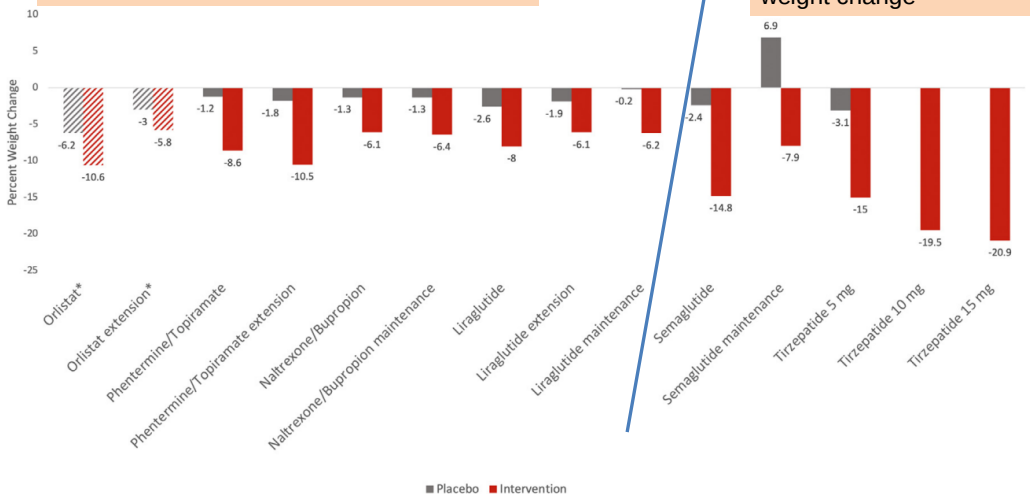
Mean % Weight Change of the FDA-approved Anti-obesity Medications

Older AOM's:
-5 to -10% placebo-corrected weight change

Newer AOM's:
-12 to -22% placebo-corrected weight change



Chakhtoura M et al. eClinicalMedicine 2023;58: 101882

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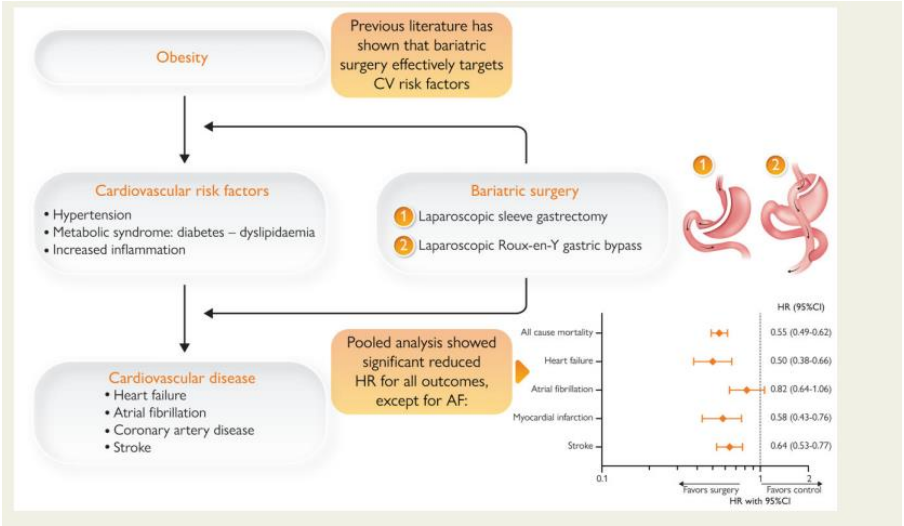
Bariatric Surgery and Reduced CV Outcomes (Meta-analysis)



van Veldhuisen SL et al. Eur Heart J. 2022; 43(20): 1955–1969.

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GLP1 Receptor Agonists: Mechanisms

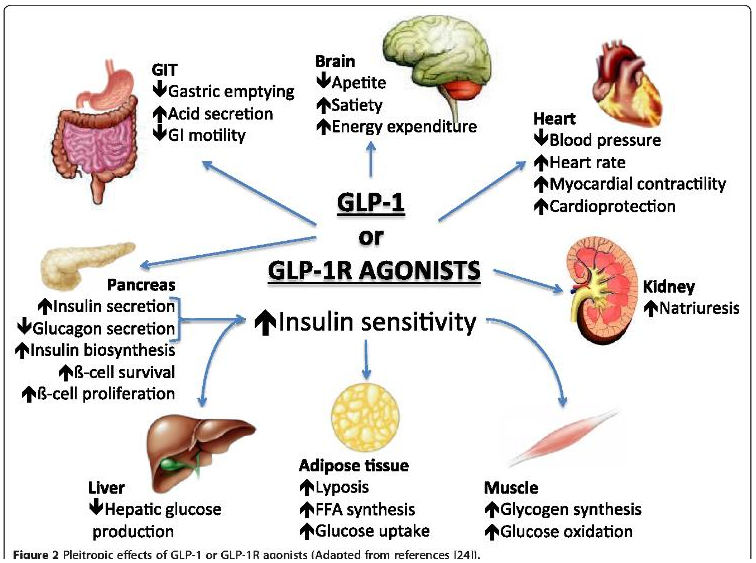

Figure 2 Pleitropic effects of GLP-1 or GLP-1R agonists (Adapted from references [24]).

Saraiva and Sposito
Cardiovascular Diabetology 2014, 13:142

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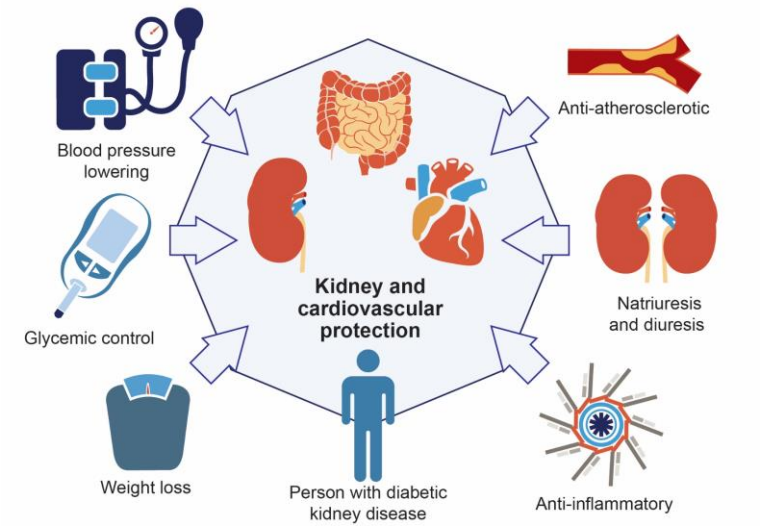
GLP1-RA: Kidney and CV Protection



Michos ED et al. Am J Prev Cardiol 2023: 100502

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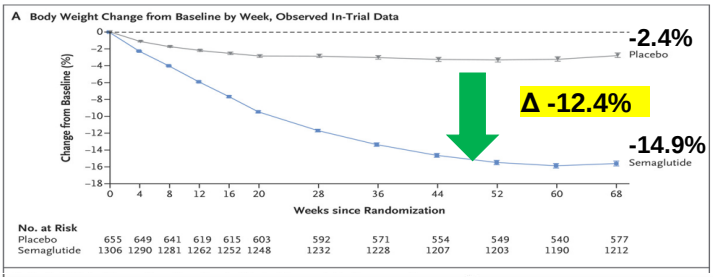
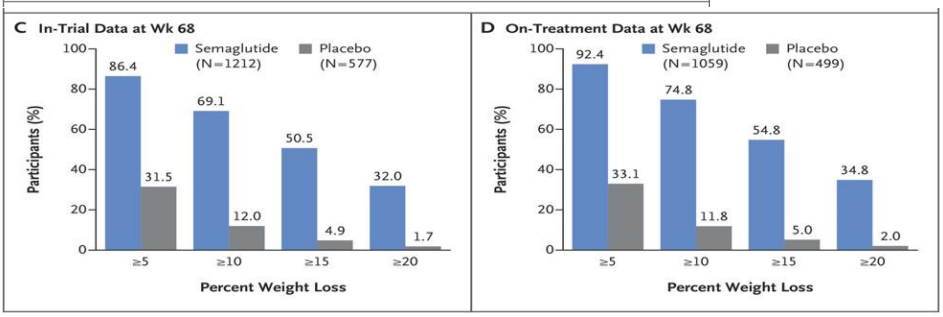
STEP 1 Trial: Semaglutide 2.4 mg/week for Overweight and Obesity



- 1961 adults with a BMI of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition) without diabetes
- Change in body weight from baseline to week 68 was −15.3 kg with semaglutide compared to −2.6 kg with placebo, for treatment difference, −12.7 kg (28 lbs).



Wilding JPH et al. N Engl J Med 2021;384:989-1002

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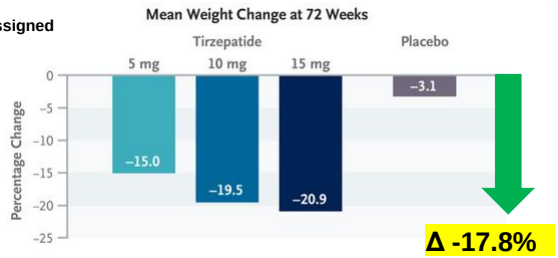
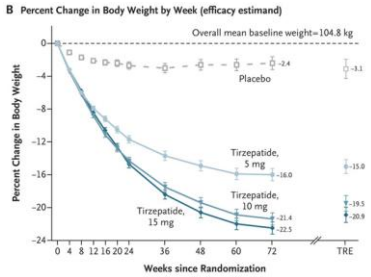
SURMONT-1: Tirzepatide (Dual GLP1/GIP Agonist) in Overweight/Obesity Among Individuals without Diabetes (n=2539, mean BMI 38.0)

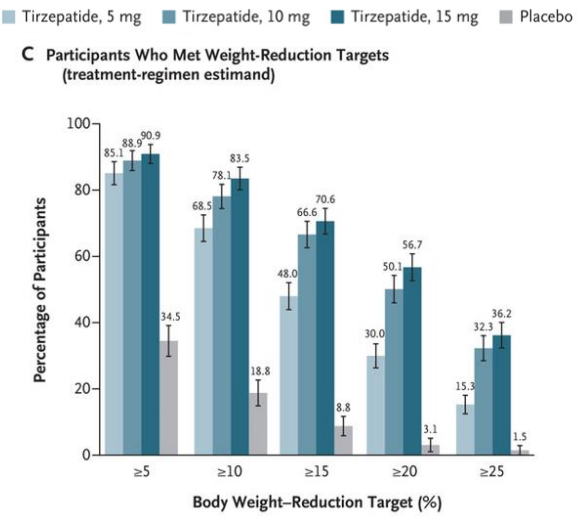
Tirzepatide 15 mg/wk: -23.6 kg (52.0 lb)

As assigned



On-treatment





Jastreboff AM et al. N Engl J Med 2022; 387:205-216

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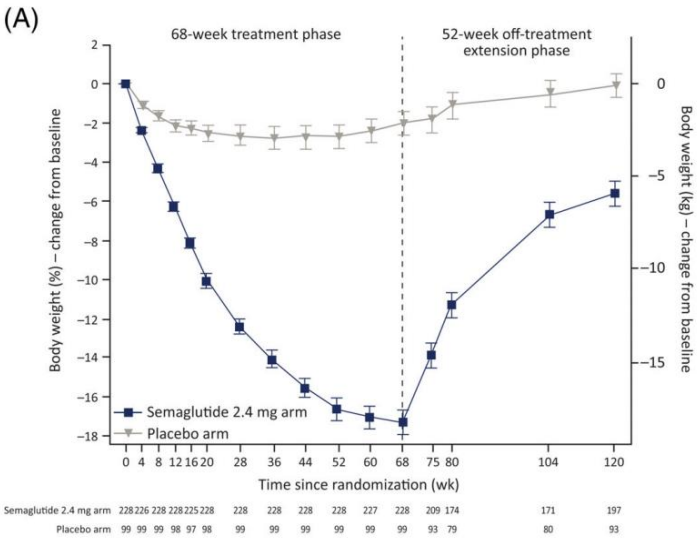
Weight Regain After GLP1-RA Cessation (STEP 1 Trial)



One year after withdrawal of once-weekly subcutaneous semaglutide 2.4 mg and lifestyle intervention, participants regained two-thirds of their prior weight loss, with similar changes in cardiometabolic variables

Wilding JPH et al. Diabetes Obes Metab. 2022;24(8):1553-1564

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Weight Loss and MACE Reduction by GLP1-RA Agent

	GLP-1 RA / Placebo
Weight loss *(mean % change in body weight)* Data from people with obesity/overweight without T2D	
MACE *(% of patients with primary composite outcome of time to first occurrence of MACE)* Data from people with T2D	

Liraglutide (s.c. 3 mg)[17] – (s.c. 0.5 and 1.0 mg)[6]	Semaglutide (s.c. 2.4 mg)[18] – (s.c. 0.5 and 1.0 mg)[20]	Tirzepatide (s.c. 5, 10 and 15 mg)[19]	Dulaglutide (s.c. 1.5 mg)[21]
–8.0% / –2.6%	–14.9% / –2.4%	–15.0% –19.5% –20.9% / –3.1%	-- / --
13.0% / 14.9%	6.6% / 8.9%	-- / --	12.0% / 13.4%
LEADER (2016) HR 0.87 (0.78-0.97)	Sustain 6 (2016) HR 0.74 (0.58-0.90)	SURPASS CVOT (on-going)	REWIND (2019) HR 0.88 (0.79-0.90)

Michos ED et al. J Am Heart Assoc 2023; 12(11):e029282.

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GLP-1 RA Meta-Analysis – CV and Non-CV Outcomes In Persons with T2D

Trials

- ELIXA
- LEADER
- SUSTAIN-6
- EXSCEL
- Harmony Outcomes
- REWIND
- PIONEER 6
- AMPLITUDE-O

Parameter	Hazard Ratio (95% CI)	NNT (95% CI)	p value	Reduction in Event
Three-point MACE	0.86 (0.80–0.93)	65 (45–130)	<0.0001	14%
Cardiovascular death	0.87 (0.80–0.94)	163 (103–353)	0.0010	13%
Fatal or non-fatal myocardial infarction	0.90 (0.83–0.98)	175 (103–878)	0.02 0	10%
Fatal or non-fatal stroke	0.83 (0.76–0.92)	198 (140–421)	0.0002	17%
Hospital admission for heart failure	0.89 (0.82 to 0.98)	258 (158 to 1422)	0.013	11%
Composite kidney outcome including macroalbuminuria	0.79 (0.73 to 0.87)	47 (37 to 77)	<0.0001	21%
Worsening of kidney function	0.86 (0.72 to 1.02)	241 (120 to −1694)†	0.089	14%

Sattar N, et al. *Lancet Diabetes Endocrinol* .2021;9(10):653-662.

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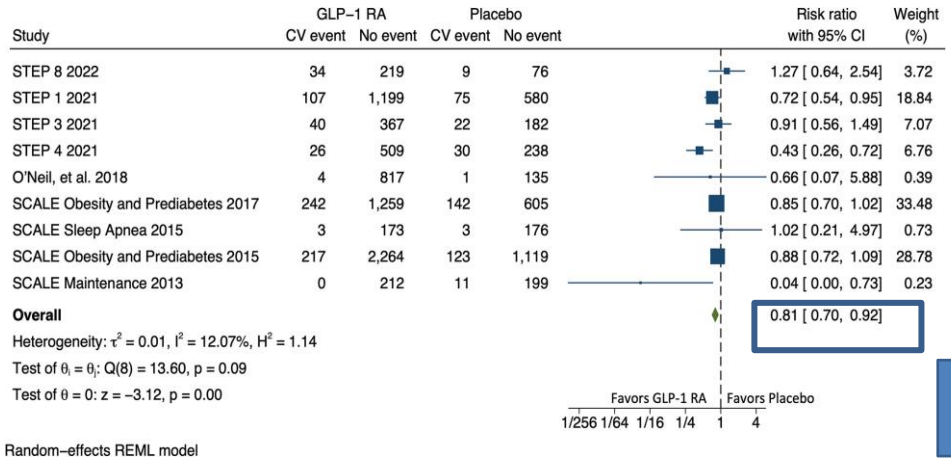
Leading up to the SELECT Trial, Earlier Data Had Suggested Lower CV Events with GLP1-RA in Overweight/Obesity without Diabetes

Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: A meta-analysis of placebo-controlled randomized trials



RR 0.81 (0.70-0.92)

Leite AR et al. Diabetes Obesity Metabolism 2022: 24 (8) :1676-1680, DOI: (10.1111/dom.14707)

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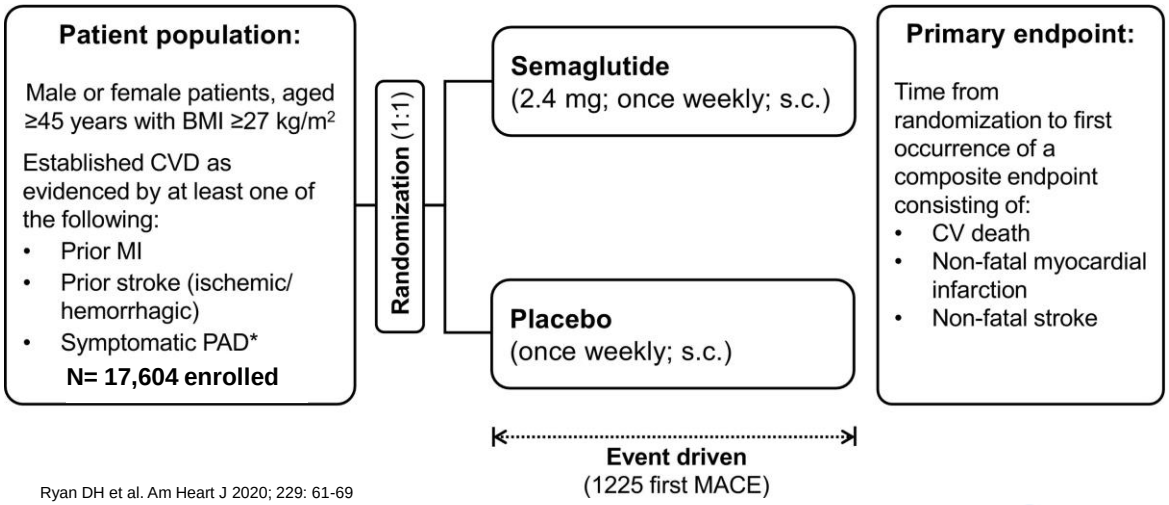
SELECT Trial: CVOT in Persons with Overweight/ Obesity but No DM at High CV Risk



Ryan DH et al. Am Heart J 2020; 229: 61-69

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SELECT Trial Baseline Characteristics

(Percent of patients unless otherwise noted)	Semaglutide (N = 8803)	Placebo (N = 8801)
Age (yrs) – mean ± SD	61.6 ± 8.9	61.6 ± 8.8
Female sex	27.8	27.5
Body Mass Index (BMI, kg/m²) – mean ± SD	33.3 ± 5.0	33.4 ± 5.0
BMI ≥ 30 kg/m²	71.0	71.9
HbA_{1c} (%) – mean ± SD	5.78 ± 0.34	5.78 ± 0.33
HbA_{1c} 5.7-6.4%	66.8	66.1
Prior MI	76.4	76.2
Prior heart failure	24.5	24.2
Systolic BP (mm Hg) – mean ± SD	131.0 ± 15.6	130.9 ± 15.3
Statin therapy	87.7	87.6
LDL Cholesterol (mg/dL) – median (IQR)	78 (61 -102)	78 (61 -102)
Triglycerides (mg/dL) – median (IQR)	134 (99 - 188)	135 (100 - 190)

From the American Heart Association Scientific Sessions 2023 presentation by Dr. Michael Lincoff
Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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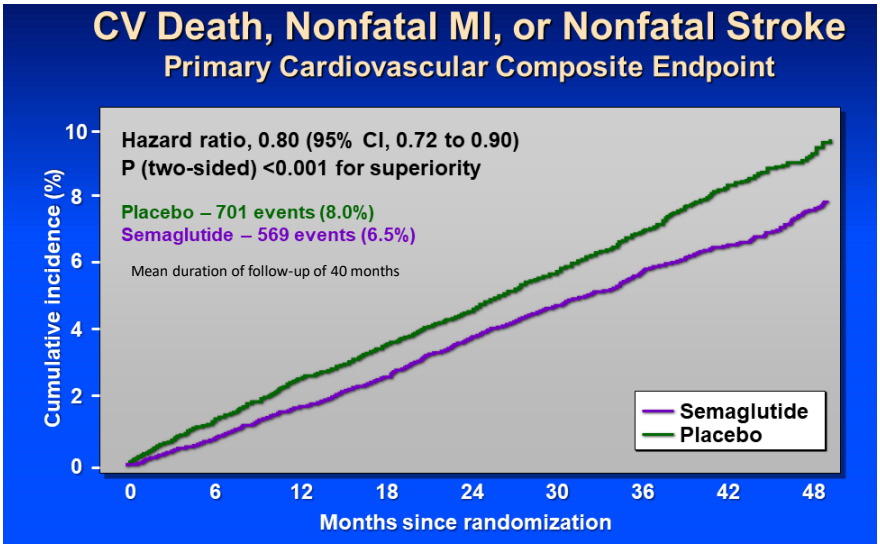
SELECT TRIAL PRIMARY ENDPOINT



From the American Heart Association Scientific Sessions 2023 presentation by Dr. Michael Lincoff
Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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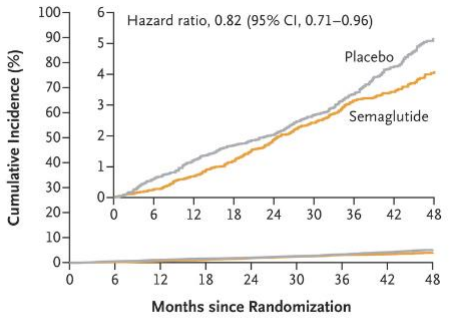
SELECT TRIAL: Semaglutide and Cardiovascular Outcomes in Persons with Overweight/Obesity but without Diabetes

Because the between-group difference in death from cardiovascular causes did not meet the required P value for hierarchical testing, results for the two subsequent end points (below) in the testing hierarchy are reported as point estimates and 95% confidence intervals.

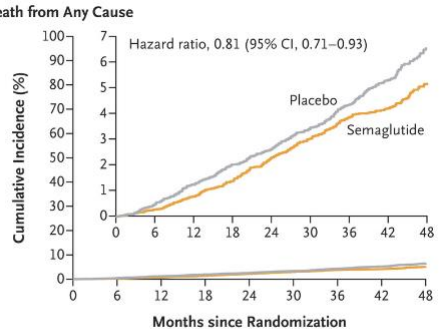
C Heart Failure Composite End Point



No. at Risk

Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

D Death from Any Cause



No. at Risk

Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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SELECT Trial: Adverse Events

There were no unexpected safety findings or greater risks of serious adverse events with semaglutide.

From the American Heart Association Scientific Sessions 2023, presentation by Dr. Michael Lincoff

Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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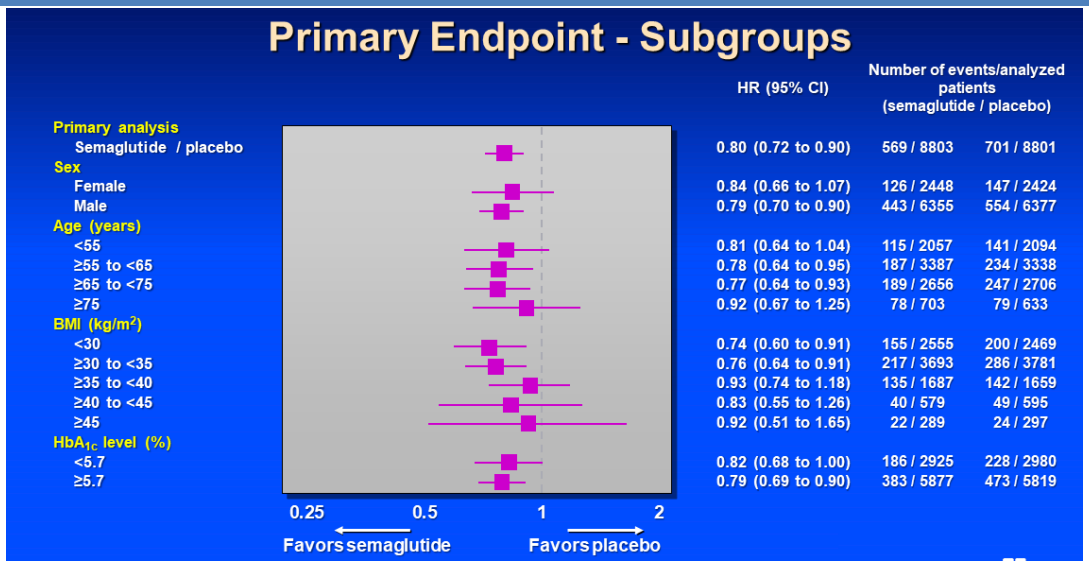
SELECT TRIAL Subgroup Analysis



From American Heart Association Scientific Sessions 2023, presentation by Dr. Michael Lincoff

Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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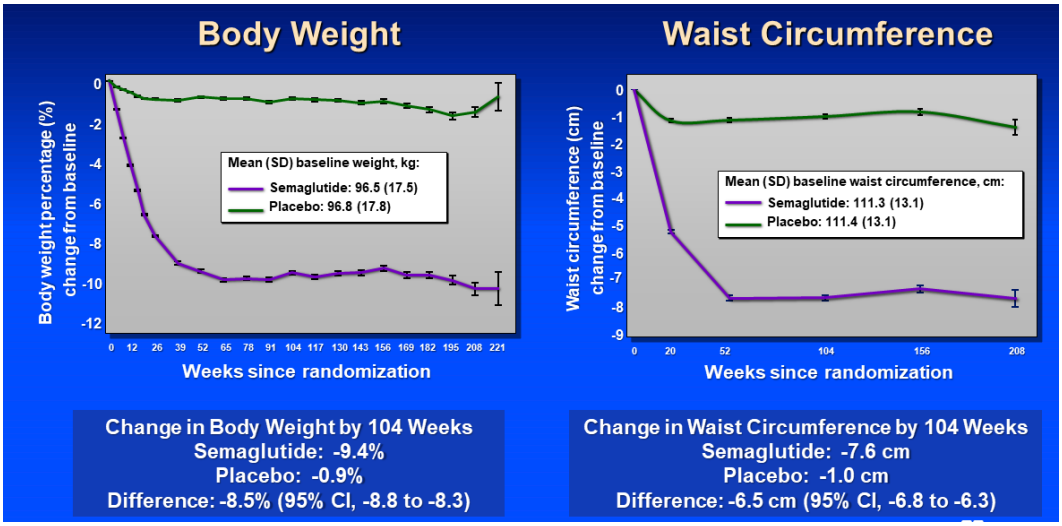
SELECT Trial Metabolic Outcomes



From American Heart Association Scientific Sessions 2023, presentation by Dr. Michael Lincoff
Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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SELECT Trial: Metabolic Secondary Endpoints

Time to first event	Semaglutide N = 8803	Placebo N = 8801	HR (95% CI)
HbA_{1c} ≥ 6.5% – % pts	3.5	12.0	0.27 (0.24 to 0.31)
HbA_{1c} ≥ 5.7% (pts with baseline <5.7%) – % pts	21.3	50.4	0.33 (0.30 to 0.36)
Change from randomization to week 104			**Difference (95% CI)**
Systolic BP – mm Hg	–3.8 (0.2)	–0.5 (0.2)	–3.3 (–3.8 to –2.9)
HbA_{1c} – percentage point	–0.3 (0.0)	0.0 (0.0)	–0.3 (–0.3 to –0.3)
hs C-reactive protein – relative change (%)	–39.1	–2.1	–37.8 (–39.7 to –35.9)
LDL-cholesterol – relative change (%)	–5.3	–3.1	–2.2 (–3.2 to –1.1)
Triglycerides – relative change (%)	–18.3	–3.2	–15.6 (–16.7 to –14.6)

From American Heart Association Scientific Sessions 2023, presentation by Dr. Michael Lincoff
Lincoff AM et al. N Eng J Med 2023; DOI: 10.1056/NEJMoa2307563

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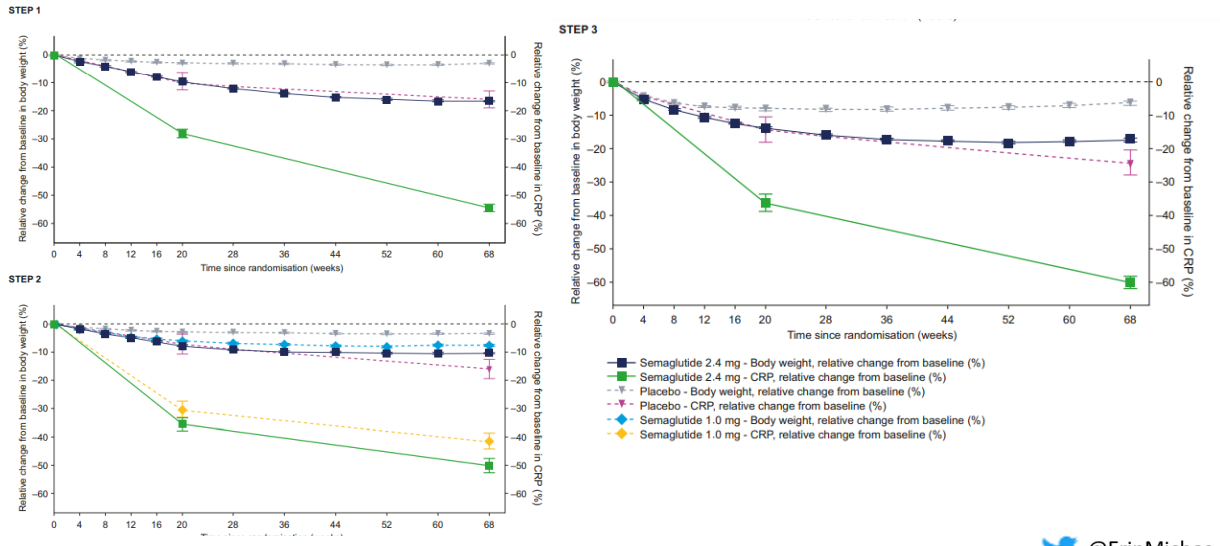
STEP Trials: Semaglutide 2.4 & 1 mg/wk Reduced hsCRP Regardless of Baseline Weight and Glycemic Status



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Verma S et al eClinicalMedicine 2023;55: 101737

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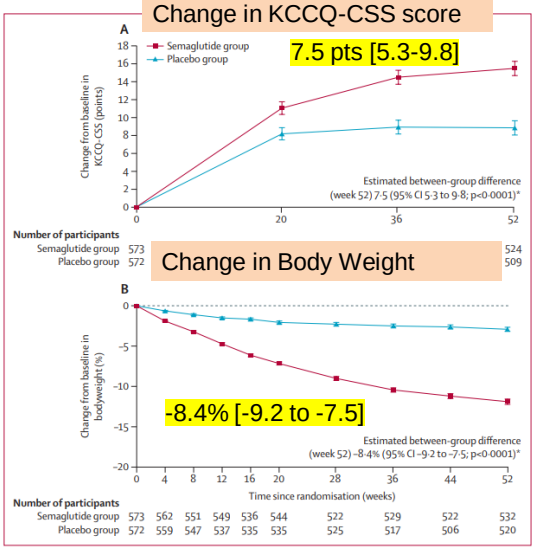
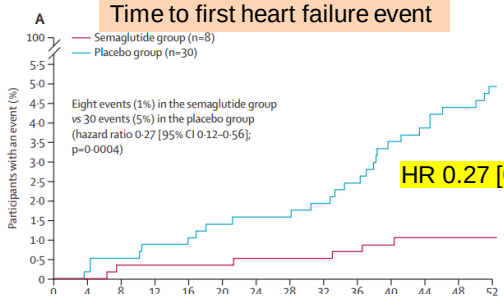
STEP-HF and STEP-HF DM Pooled Results in Pts with HFpEF & BMI ≥30 (n=1145)]

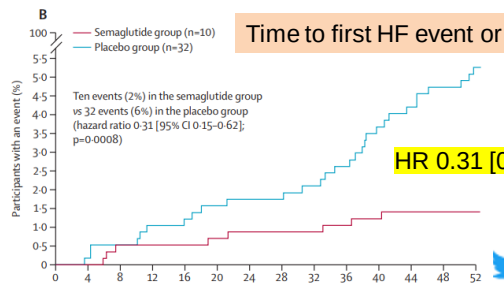
Change in KCCQ-CSS score



Time to first heart failure event



Time to first HF event or CV death



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Butler J et al Lancet 2024; 403: 1635–48

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Semaglutide – Updated FDA Label

Semaglutide indicated in combination with a reduced calorie diet and physical activity:

- **To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.**
- To reduce excess body weight and maintain weight reduction long term in:
  - Adults and pediatric patients aged 12 years and older with obesity
  - Adults with overweight in the presence of at least one weight-related comorbid condition

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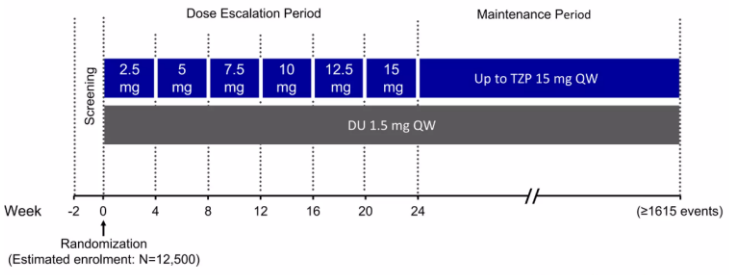
SURPASS CVOT:

Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease:

A study to compare the effect of tirzepatide (maximum tolerated dose) vs dulaglutide 1.5 mg on major cardiovascular events in participants with T2D with established CVD



SURPASS-CVOT. Available at: https://clinicaltrials.gov/ct2/show/NCT04255433. Accessed May 2020

Table II. Baseline clinical characteristics in SURPASS-CVOT.

	SURPASS-CVOT (*N* = 13,299)
Age, years	64.1 ± 8.8
Sex, female	3849 (28.9)
Geography	
North America	1955 (14.7)
South America	3833 (28.8)
Europe	6149 (46.2)
Asia-Pacific	1,362 (10.2)
Weight, kg	92.5 ± 18.8
BMI, kg/m^2	32.6 ± 5.5
History	
Coronary artery disease	8,649 (65.0)
Myocardial infarction	6,288 (47.3)
Coronary revascularization procedure	7,630 (57.4)
Stroke	2,541 (19.1)
Peripheral artery disease	3,369 (25.3)
Hypertension	11,986 (90.1)
Dyslipidemia	1,1406 (85.8)
Current tobacco use	1,978 (14.9)
Diabetes duration, years	14.7 ± 8.8
Systolic blood pressure, mm Hg	135.0 ± 15.7
Diastolic blood pressure, mm Hg	77.7 ± 9.7
HbA1c, %	8.4 ± 0.9
eGFR (CKD-EPI), mL/Min/1.73 m^2	76.5 ± 21.3
<60 mL/Min/1.73 m^2	3,029 (22.8)
UACR, mg/g	22.0 (9.0, 83.0)
Microalbuminuria	4,179 (32.0)
Macroalbuminuria	1,503 (11.5)

Nicholls SJ et al. Am Heart J 2024

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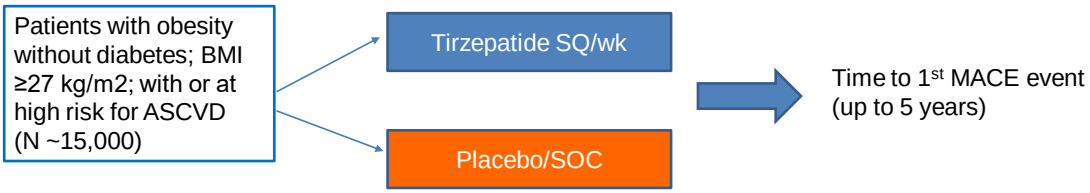
SURMOUNT-MMO: Tirzepatide (Dual Agonist) vs Placebo in Adults with Obesity with or at High Risk for ASCVD but without Diabetes

- International, randomized, double-blind, placebo-controlled phase III trial
- **Primary Outcome**: Time to first occurrence of death/MI/stroke/coronary revascularization/HF
- **Select secondary outcomes**: time to T2D onset, composite kidney death/ESKD/eGFR decline, HF events, body weight change



NCT05556512

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GLP1-RA Mechanisms for Cardioprotection

- Mechanisms of CV risk reduction with semaglutide (in SELECT) remain speculative but may include those related to physiological benefits from reduction of metabolically dysfunctional body fat and/or actions of semaglutide other than weight loss

From the American Heart Association Scientific Sessions 2023 presentation by Dr. Michael Lincoff

Ryan DH et al. Am Heart J 2020; 229: 61-69

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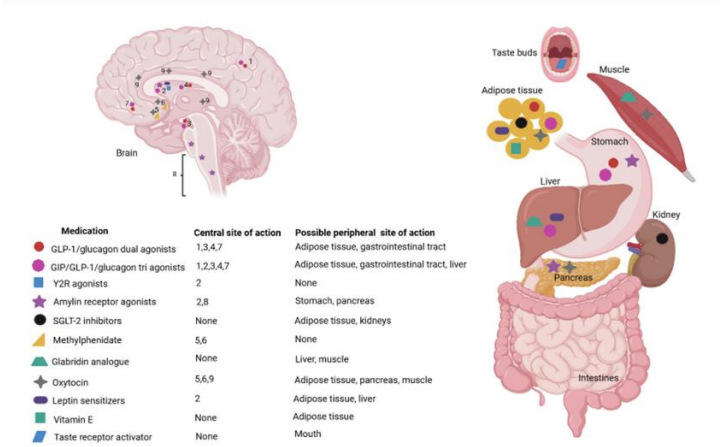
AOM Pipeline



Medication	Central site of action	Possible peripheral site of action
GLP-1/glucagon dual agonists	1,3,4,7	Adipose tissue, gastrointestinal tract
GIP/GLP-1/glucagon tri agonists	1,2,3,4,7	Adipose tissue, gastrointestinal tract, liver
Y2R agonists	2	None
Amylin receptor agonists	2,8	Stomach, pancreas
SGLT-2 inhibitors	None	Adipose tissue, kidneys
Methylphenidate	5,6	None
Glabridin analogue	None	Liver, muscle
Oxytocin	5,6,9	Adipose tissue, pancreas, muscle
Leptin sensitizers	2	Adipose tissue, liver
Vitamin E	None	Adipose tissue
Taste receptor activator	None	Mouth

Fig. 4: **Site of action of drugs under development for treatment of obesity.** (1) parietal cortex, (2) hypothalamus, (3) insula, (4) putamen, (5) nucleus accumbens, (6) striatum, (7) orbitofrontal cortex, (8) hindbrain, (9) mesolimbic area. GLP-1/glucagon dual agonists, GIP/GLP-1 dual agonists, Y2R, amylin receptor agonists, methylphenidate, oxytocin, and leptin sensitizers act centrally to reduce food intake. Few drugs act solely peripherally: SGLT-2 inhibitors on the kidney; Gladribin on liver and muscle; Vitamin E on adipose tissue. GIP, Gastric inhibitory polypeptide; GLP-1, Glucagon receptor agonist; SGLT2, Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors; Y2R, Y2-receptor. Tesofensine is not included in the figure as we did not identify any related ongoing study. This figure was created using BioRender (https://biorender.com/).

Chakhtoura M et al. eClinicalMedicine 2023;58: 101882

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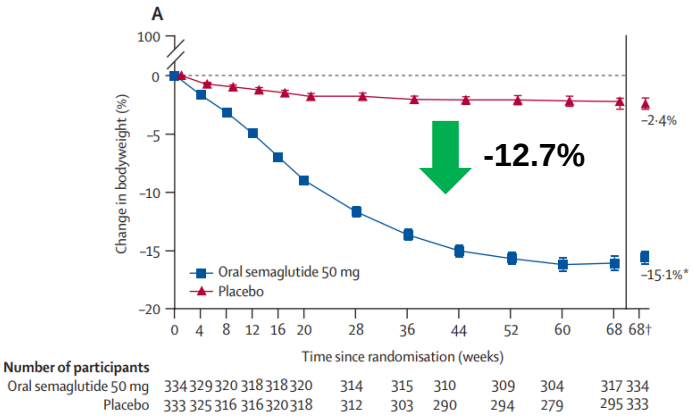
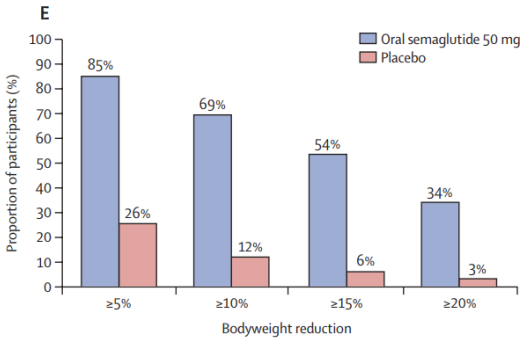
Oral Semaglutide for Weight Management (OASIS-1)

Phase 3: 667 adults with obesity or overweight + ≥1 comorbidity but no DM





17.4% if all people adhered to treatment

Knop FK et al. The Lancet 2023; 402: 705-719. DOI: (10.1016/S0140-6736(23)01185-6)

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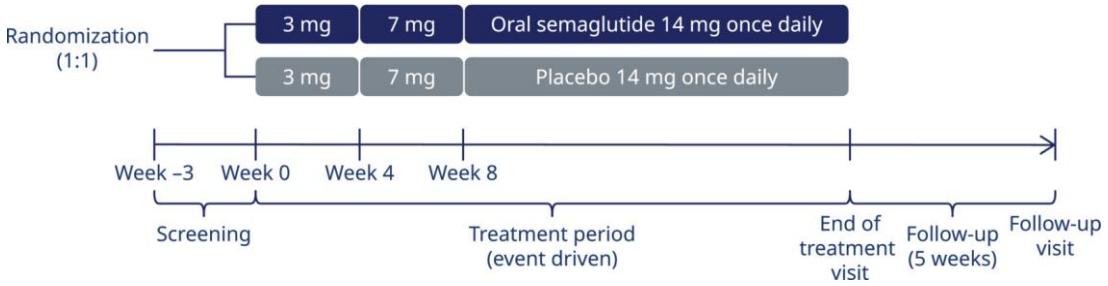
SOUL Trial: Oral Sema and MACE in T2D

Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial

N=9650



The primary trial outcome is time from randomization (week 0) to first occurrence of adjudication-confirmed MACE (a composite outcome consisting of CV death, nonfatal MI or nonfatal stroke).

McGuire DK et al. Diabetes Obesity Metabolism, First published: 21 March 2023, DOI: (10.1111/dom.15058)

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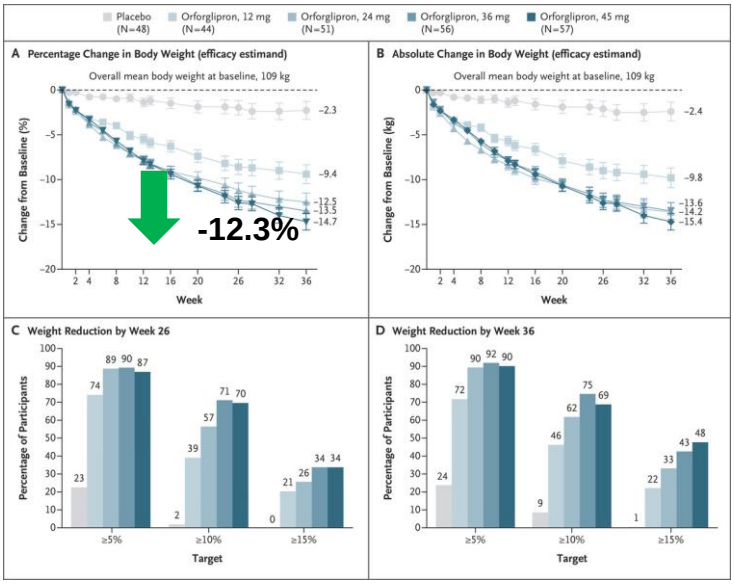
Orforglipron: an Oral Nonpeptide GLP-1 RA



Phase 2 trial : 272 adults with obesity or overweight + ≥1 comorbidity but no DM

Dosed orally once daily

CVOT in progress
A Study of Daily Oral Orforglipron (LY3502970) Compared With Insulin Glargine in Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk (ACHIEVE-4)
NCT05803421

Wharton et al. N Engl J Med 2023.
DOI: 10.1056/NEJMoa2302392

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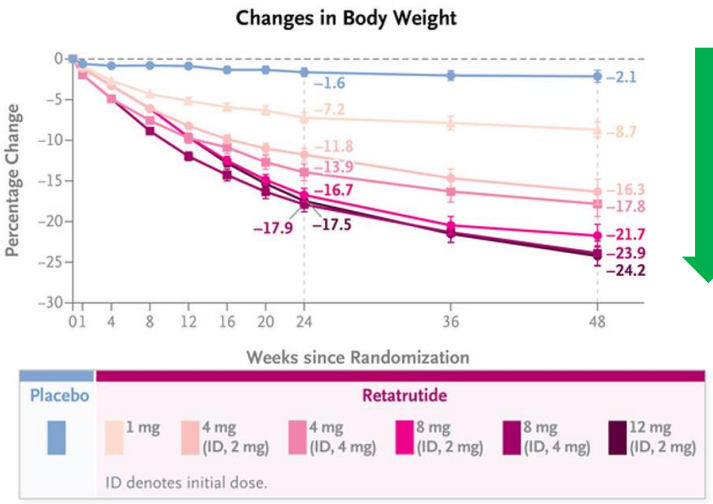
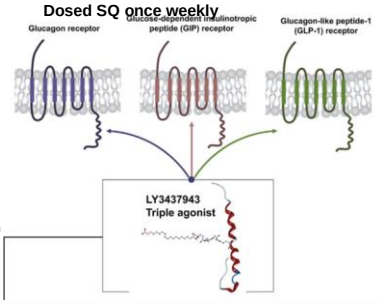
Retatrutide: A Triple Agonist (Glucagon, GIP, GLP1)

Phase 2 trial : 338 adults with obesity or overweight + ≥1 comorbidity but no DM



-22.1%



CONCLUSIONS

In adults with obesity without diabetes, once-weekly treatment with subcutaneous retatrutide led to substantial, dose-dependent reductions in weight at 24 and 48 weeks.

TRIUMPH 3 will study efficacy & safety of retatrutide in persons with obesity and established CVD. Primary outcome: weight change (not a CVOT). (n=1800) NCT05882045

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Jastreboff AM et al. N Engl J Med 2023;389:514-526.

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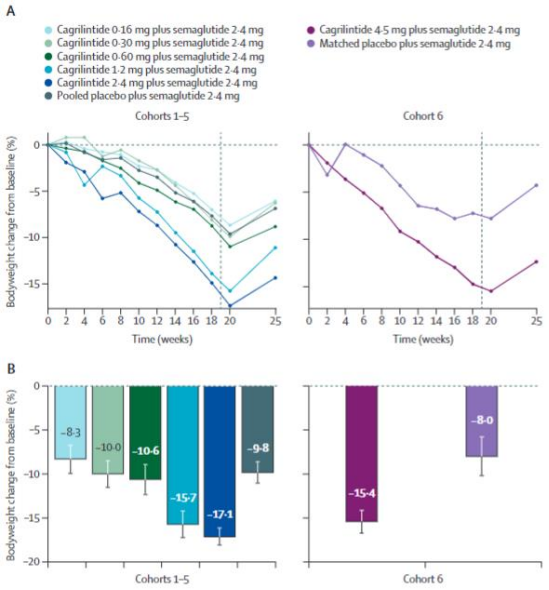
Cagrilintide/Semaglutide



-17% weight change at 20 weeks

Phase 1B trial of Cagrilintide, a long-acting amylin analogue, with semaglutide 2.4 mg, a GLP1-RA

CVOT in progress

A Research Study to See the Effects of CagriSema on Heart Disease in People Living With Obesity and Diseases in the Heart and Blood Vessels (REDEFINE 3) (n=7000). NCT05669755

Enebo LB et al. Lancet 2021; 397: 1736–48

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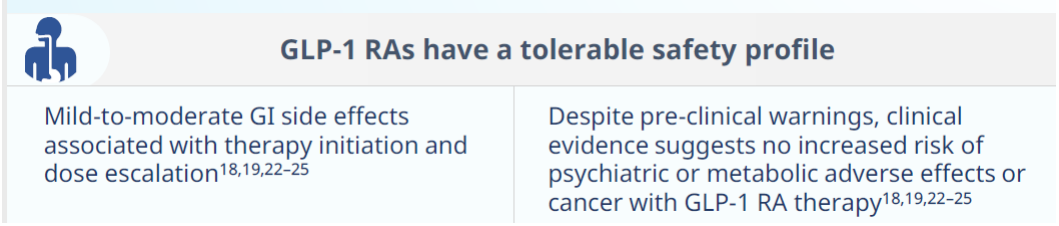
Adverse Effects with GLP1-RAs

- GI side effects, such as nausea, are commonly reported upon initiation of GLP-1 RA treatment
- As many as 75% will have GI side effects
- however, these often diminish within the first month of treatment and can be mitigated through a gradual dose-escalation period and temporary dietary adjustments



- Increased risk of medullary thyroid cancer seen in rodents with GLP1-RA
- This associated has not been seen yet in humans
- Medullary thyroid cancer is extremely rare in humans, with 976 cases diagnosed from 1992 to 2006 in the United States, compared with 36,583 cases of papillary and 4,560 cases of follicular cancer.

Michos ED et al. J Am Heart Assoc 2023; 12(11):e029282.

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Shared Decision Making for AOMs

- Healthy lifestyle measures are always reinforced and encouraged
- There are FDA approved medications that help people lose more weight more than diet/exercise alone
- Involve patient in decision making: cost, side effects, how much weight loss is needed, potential side benefits of medication.
- These medicines only work as long as the person takes them, so person needs to be open to long term use.
- Semaglutide has been shown to reduce adverse cardiovascular outcomes in persons with overweight/obesity and established CVD as well as improve quality of life in in patients with obesity and HFpEF
  - CVOTs for other GLP1-RA and/or other populations are underway

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Conclusions

- Obesity is associated with an increased risk of CVD and CV-associated mortality.
- Obesity is a chronic, serious life threatening disease, but treatments exist
- GLP-1 RAs should be considered by cardiologists and other HCPs
  - as a treatment option for obesity (chronic weight management)
  - to reduce CVD risk in patients with T2D
  - to reduce CVD events in persons with overweight of obesity and established CVD
- Improving the recognition and understanding of GLP-1 RA therapy among HCPs may re-motivate them in supporting patients in losing weight
- Mild-to-moderate GI side effects associated with therapy initiation and dose escalation.
- Prior-auths, insurance plan exclusions, and financial barriers remain a challenge in clinical practice for implementation of GLP1-RA therapy

Michos ED et al. J Am Heart Assoc 2023; 12(11):e029282.

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All of the following are TRUE statements about EXCEPT:

A. GLP-1RA improves heart failure symptoms in patients with HFpEF
B. Weight regain is common after cessation of GLP1-RA therapy
C. In absence of diabetes, the MACE reduction with semaglutide was only seen in persons with BMI >30
D. Majority of patients on GLP1-RA therapy experience some GI side effects

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