Cardiovascular Prevention in Patients with Obesity: Understanding the Role of GLP1RA

Matt Cavender, MD, MPH
Associate Professor of Medicine
Director, Cardiovascular Clinical Trials
University of North Carolina
Chapel Hill, NC

CONTINUING EDUCATION COMPANY

1

Disclosure

Consultant: Abbvie; Bayer Pharmaceuticals; CSL Behring; Faraday Pharma; New Amsterdam Pharma; Novo Nordisk

Research Grant: Amgen; Boehringer Ingelheim; CSL Behring; Janssen; Massachusetts General Hosp/PCORI; Novartis; Novo Nordisk

CONTINUING EDUCATION COMPANY

2

UNC SCHOOL OF MEDICINE

3

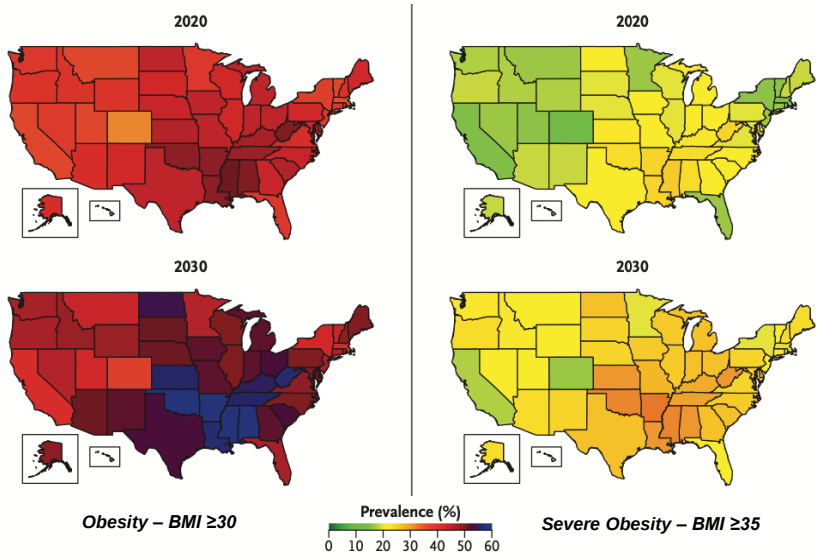
Objectives

UNC SCHOOL OF MEDICINE

- Review the global prevalence of obesity, diabetes, and CVD and the strong relationship between these conditions
- Understand the benefits of current guideline based therapy with a GLP1RA
- Discuss common questions and challenges that have prevented more frequent utilization of GLP1RA

4

Increasing Prevalence of Obesity in US



N Engl J Med 2019;381:2440-50

5

Global Prevalence of Obesity and CVD

..... Because the cardiovascular disease affects a third of adults in the world, it is the largest epidemic ever known to mankind (Yusef et al. Lancet 2015).

523 million people had **CVD** in 2019 (globally)

32% of all global **deaths** are from **CVD**

85% of all CVD deaths are due to **heart attacks and stroke**

1bn people with **obesity** predicted by 2030

Conditions included in CVD definition may vary.
CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.
WHO Fact sheet – CVDs. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/; Roth GA et al. J Am Coll Cardiol 2017;70(1):1–25; WHO, Obesity & Overweight. 2020. Available from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed November 2020; GBD 2015 Obesity Collaborators. N Engl J Med 2017; 377(1):13–27.

6

Global Prevalence of Obesity Is Expected to Reach 1 Billion by 2030 (Among Adults)

UNC SCHOOL OF MEDICINE

764
million people
live with obesity

Obesity prevalence defined by BMI (in adults)	2020		2025		2030	
	%	n (million)	%	n (million)	%	n (million)
Obesity (Class I, II and III) ≥30kg/m^2	15	764	16	892	18	1025
Obesity (Class II and Class III) ≥35kg/m^2	5	238	5	284	6	333
Obesity (Class III) ≥ 40 kg/m^2	2	77	2	93	2	111

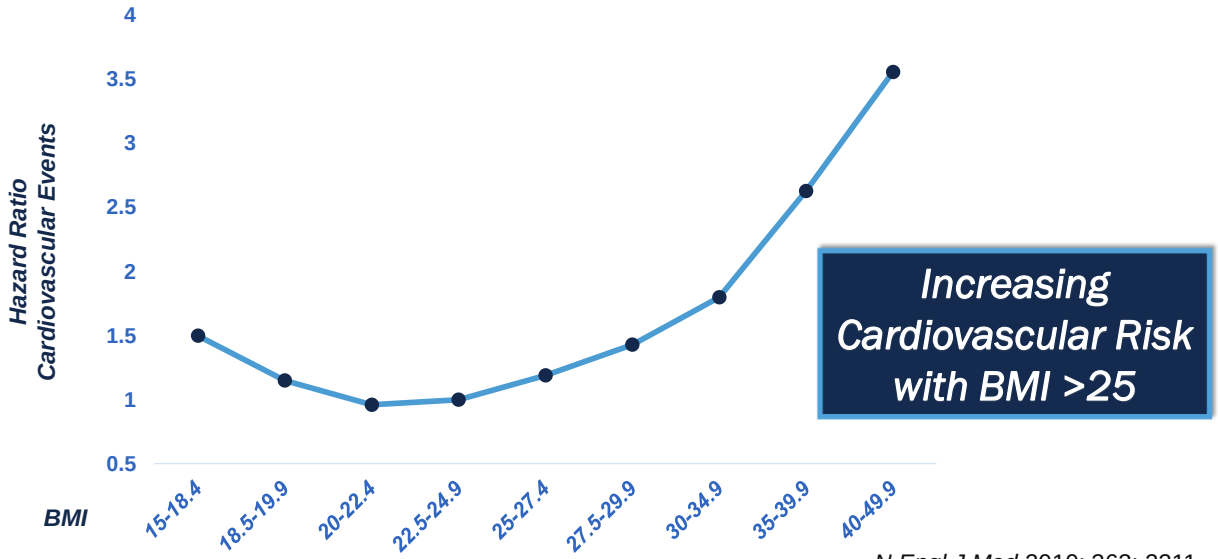
WHO, World Health Organization.
World Obesity Federation, World Obesity Atlas 2022. Available at: https://www.worldobesityday.org/policy-makers (accessed August 2022).

7

Relationship Between BMI and CV Events

Data from 19 Prospective Studies Including 1.46 Million Adults

UNC SCHOOL OF MEDICINE



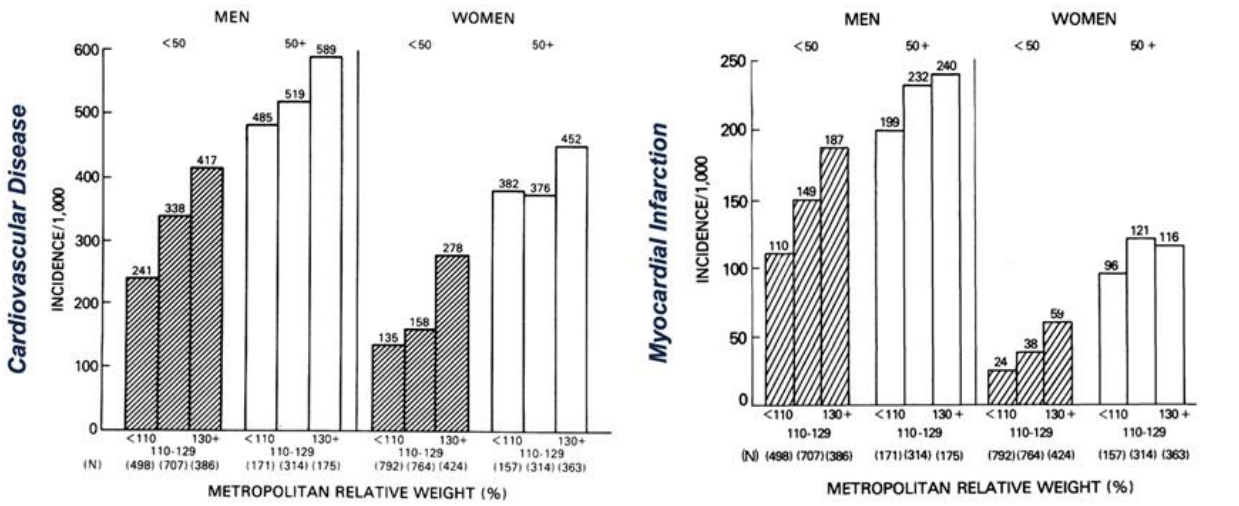
N Engl J Med 2010; 363: 2211

8

Obesity Is a Risk Factor for Cardiovascular Disease

n=5,209 from Framingham Heart Study Followed for 26 Years

UNC SCHOOL OF MEDICINE



Hubert et al. Circulation. 1983; 67:968–977

9

Effect of Potentially Modifiable Risk Factors Associated with MI in 52 Countries: The INTERHEART Study

- Standardized case control study of AMI (52 countries)
  - 15,152 cases – 14,820 controls
  - 9 risk factors account for 90% of population attributable risk (PAR) in men, 94% in women

Risk factor	Odds ratio	PAR
ApoB/A1 (quintiles)	3.25	49.3% (top 4 vs. last)
Smoking	2.87	35.7%
Psychosocial	2.67	32.5%
Diabetes	2.37	9.9%
HTN	1.91	17.9%
Obesity (quartiles)	1.62	20.1% (top 3 vs. last)
Daily fruits/vegetables	0.70	13.7% (lack of)
Regular physical activity	0.86	12.2% (lack of)
Daily EtOH	0.91	6.7% (lack of)

UNC SCHOOL OF MEDICINE

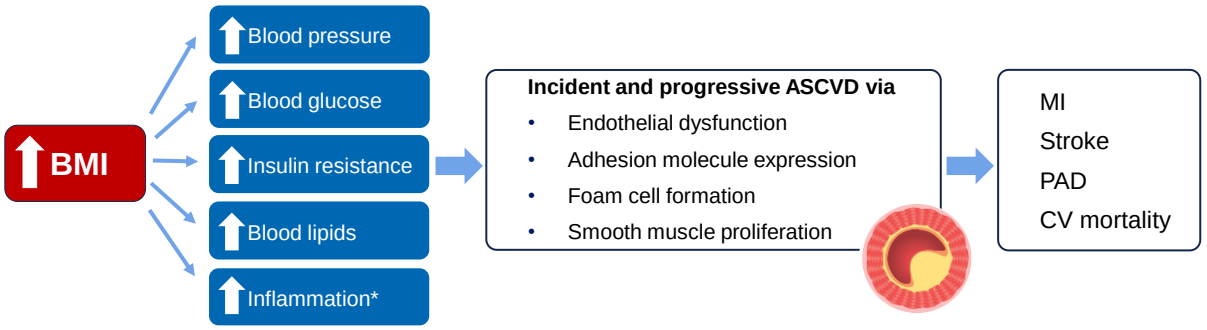
Yusuf S et al. *Lancet* 2004; 364:937

10

Obesity Is a Major Determinant of Residual CV Risk

UNC SCHOOL OF MEDICINE

Excess weight promotes cardiovascular disease via multiple mechanisms



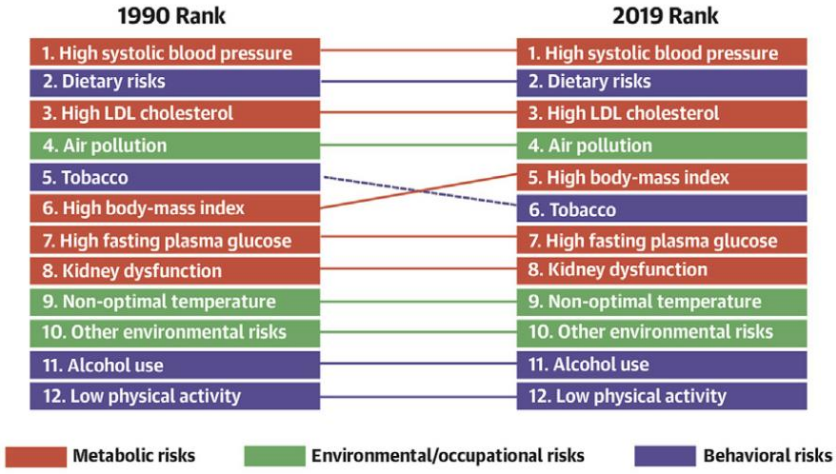
*Increased TNFa, CRP, IL-6 and free fatty acids CRP, C-reactive protein; CV, cardiovascular; IL-6, interleukin-6; MI, myocardial infarction; PAD, peripheral arterial disease; TNFa, tumour necrosis factor alpha. Burke et al. *Arch Intern Med* 2008;168:928–35; Ayer et al. *Eur Heart J* 2015;36:1371–6; Ross R. *Am Heart J* 1999;138(5 Pt 2):S419–20; WHO Global atlas on cardiovascular disease prevention and control. 2011. Available at: https://apps.who.int/iris/handle/10665/44701 (accessed November 2022).

11

CVD Burden Attributable to Modifiable Risk Factors

UNC SCHOOL OF MEDICINE

Estimates from the Global Burden of Disease Survey



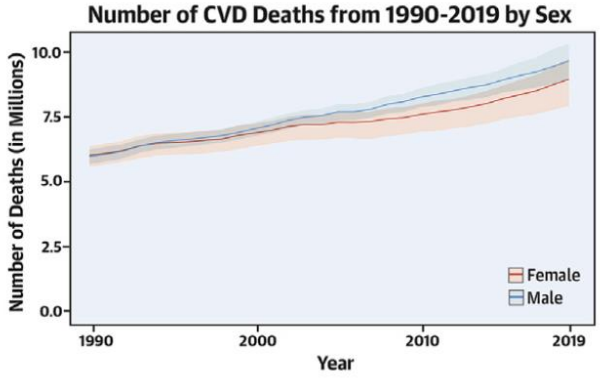
J Am Coll Cardiol 2020;76:2982

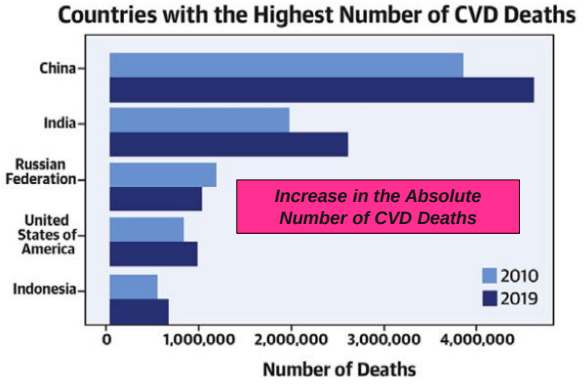
12

Estimates from the Global Burden of Disease Survey

UNC SCHOOL OF MEDICINE

Number of CVD Deaths



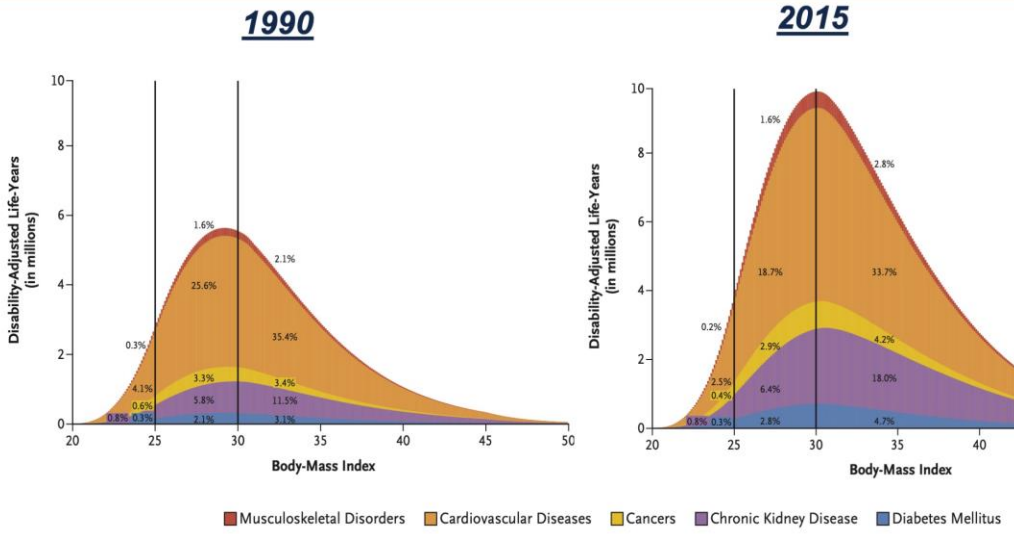


J Am Coll Cardiol 2020;76:2982

13

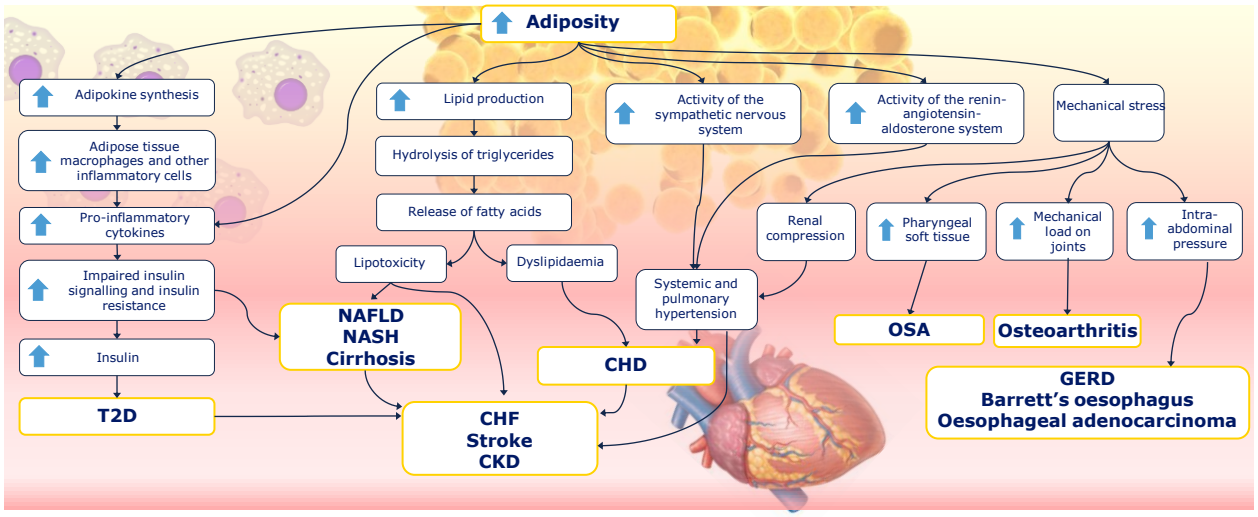
Increasing Obesity Related CV Disability

UNC SCHOOL OF MEDICINE



14

Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases



CHD, coronary heart disease; CHF, coronary heart failure; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic stereohepatitis; OSA, obstructive sleep apnea; T2D, type 2 diabetes.
Heymsfield SB and Wadden TA. *NEJM* 2017;376:254–66.

15

AHA Scientific Statement on Obesity and CV Disease

AHA SCIENTIFIC STATEMENT

Obesity and Cardiovascular Disease

A Scientific Statement From the American Heart Association

1. ***Obesity is a multifactorial disease***
2. WHO defines obesity as a BMI ≥30 kg/m^2
3. Additional metrics such as waist circumference, visceral adipose tissue, waist circumference to height, waist-to-hip ratio (WHR) can be used to identify obesity
4. Exercise may reduce visceral adiposity
5. ***The impact of obesity on CV health starts in childhood***
6. Visceral adiposity promotes systemic and vascular inflammation
7. Cardiac testing, particularly imaging, in the setting of obesity can be challenging
8. ***For many CV events, a u-shaped association between BMI and adverse events has been observed***
9. Obesity may account for 20% of atrial fibrillation (AF) cases

16

Obesity: An Overview of the Disease

WHO Definition - BMI ≥ 30

Specific Causes

- Genetic - mutations in the melanocortin-4 receptor gene are the most common cause of monogenic obesity
- Environmental – sedentary lifestyle plus high caloric food
- Physiologic – decreased metabolic rates
- Sociologic – food/alcohol as cornerstone of social interactions and entertainment
- Wealth – increased food supply in developed world
- Psychologic – coping mechanisms

Heymsfield SB, Wadden TA. N Engl J Med 2017;376:254-66

17

Obesity: An Overview of the Disease

- 39% to 49% of the world's population (2.8–3.5 billion people) are estimated to be either overweight or obesity.
- Estimated that ***603.7 million*** adults have obesity - Global Burden of Disease Obesity Collaborators
- Prevalence of obesity has doubled between 1980 and 2015 in 73 countries
- Elevated BMI accounted for 4.0 million deaths in 2015 (>75% from cardiovascular disease)

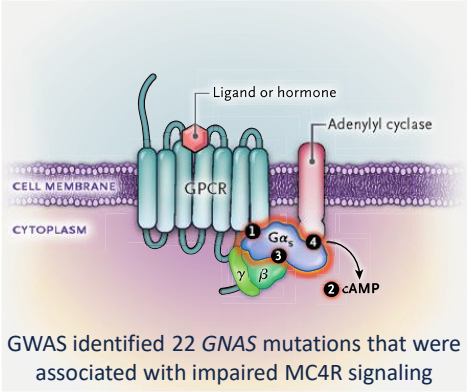
Heymsfield SB, Wadden TA. N Engl J Med 2017;376:254-66

18

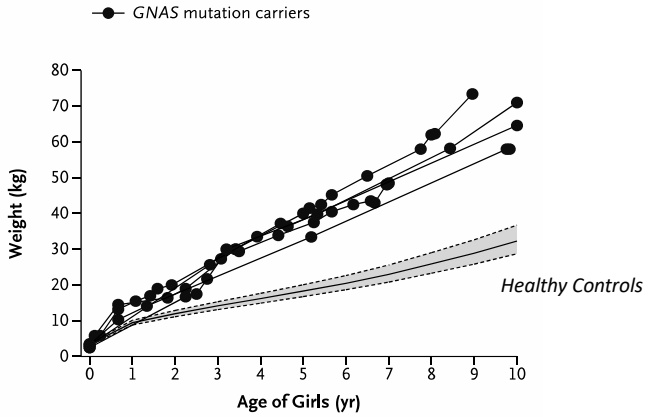
Obesity Is More than Lack of Will Power...

N=2,456 Children With Severe Obesity

Mutations in the proopiomelanocortin (*POMC*)
gene result in the lack of activation of the melanocortin-4 receptor (MC4R)
Causing hyperphagia and severe early-onset obesity



GWAS identified 22 *GNAS* mutations that were associated with impaired MC4R signaling



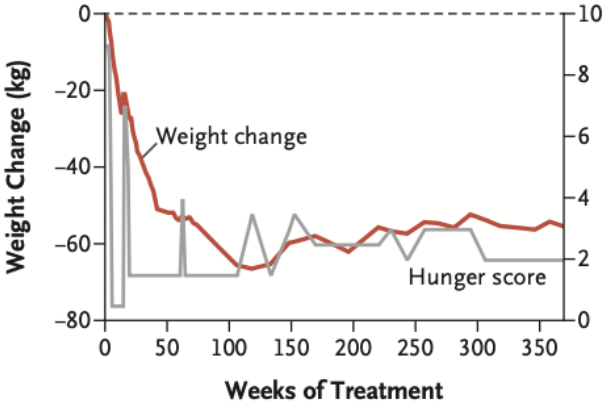
N Engl J Med 2021; 385:1581-92

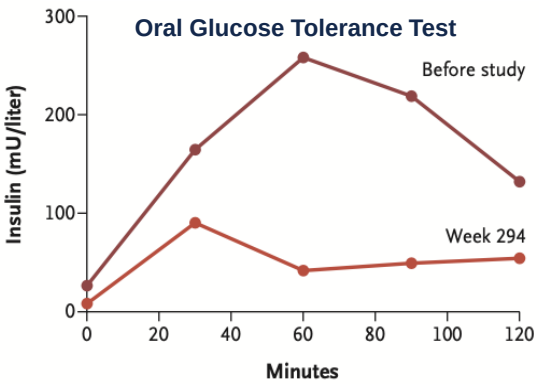
19

Obesity Is More than Lack of Will Power...

Effect of MC4R Agonist in Pts with POMC Gene Mutation

Mutations in the proopiomelanocortin (*POMC*)
gene result in the lack of activation of the melanocortin-4 receptor (MC4R)
Causing hyperphagia and severe early-onset obesity

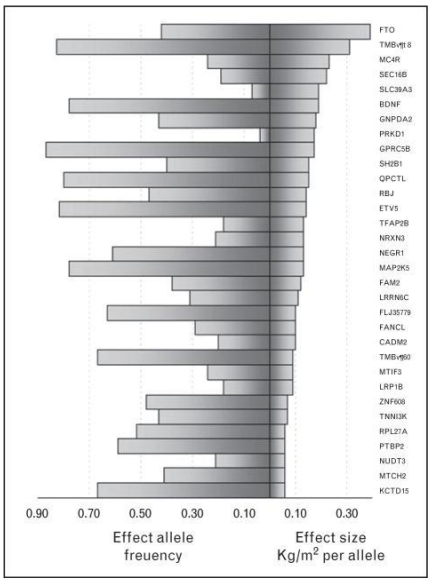




Kühnen, Clément. N Engl J Med 387; 9: 852

20

Effect Size and Frequency of Some Obesity Gene Variants

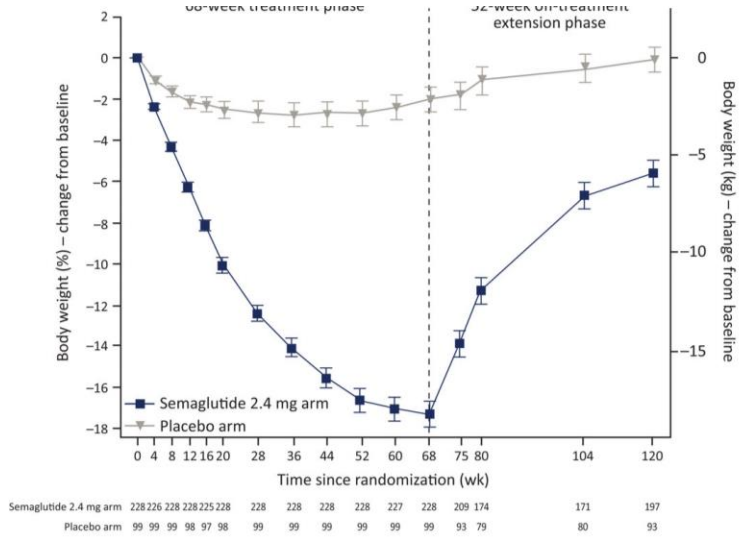


Qi. Curr Opin Lipidol 2014;25:27–34.

21

Obesity Is More than Lack of Will Power...

High Relapse Rate in Obesity



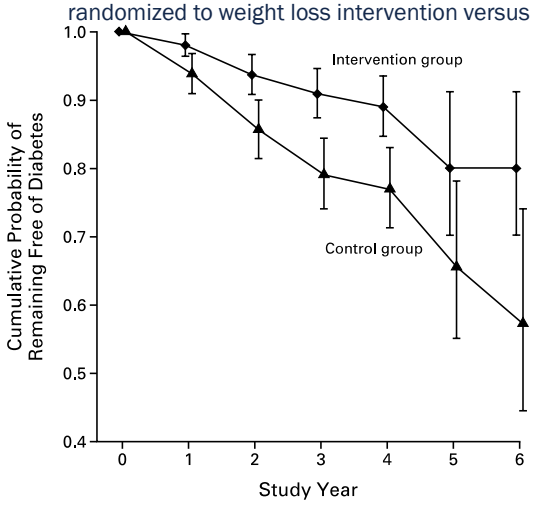
Obesity is a lifelong, chronic disease and needs for long-term treatment strategies

Wilding et al. Diabetes Obes Metab. 2022;24:1553

22

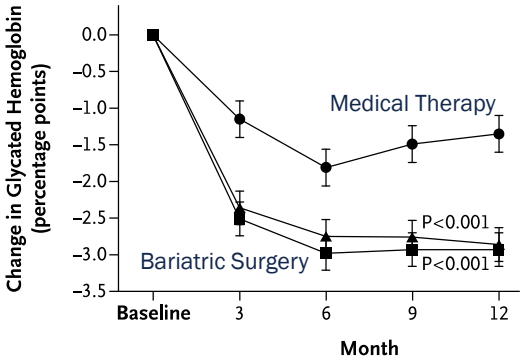
Impact of Weight Loss on Diabetes Metrics

n=522 overweight pts with impaired fasting glucose randomized to weight loss intervention versus control



N Engl J Med 2001; 344: 229

n=150 obese pts with T2DM in STAMPEDE



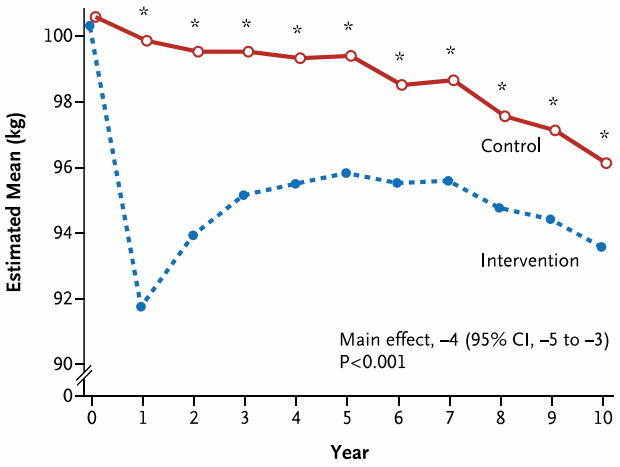
Value at Visit					
Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6

N Engl J Med 2012; 366: 1567

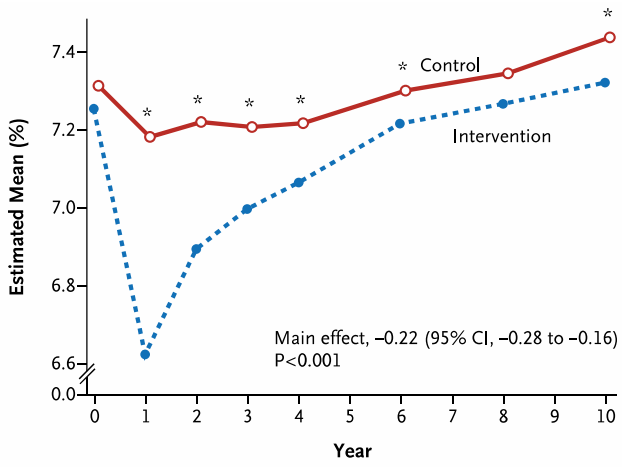
23

Weight Loss Can Improve Glycemic Control (LOOK AHEAD)
n=5,145 Pts Randomized to Intensive Risk Factor Management or Control

Weight

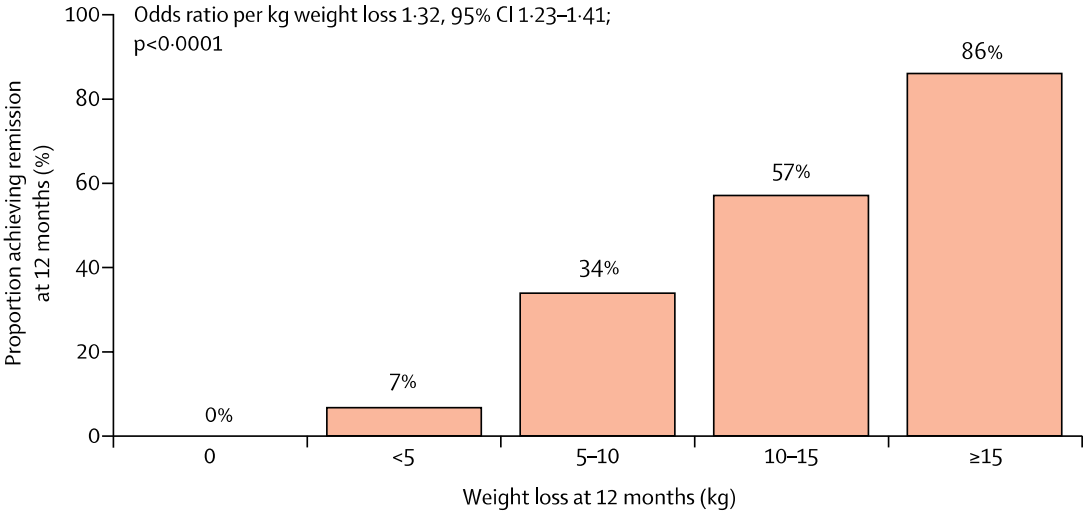


HbA1c



24

Weight Loss Results in Diabetes Remission (DIRECT)

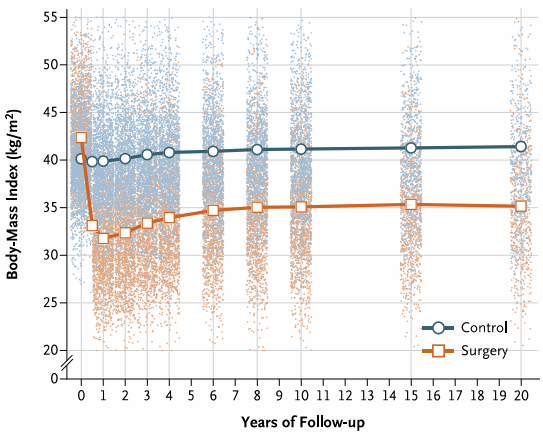


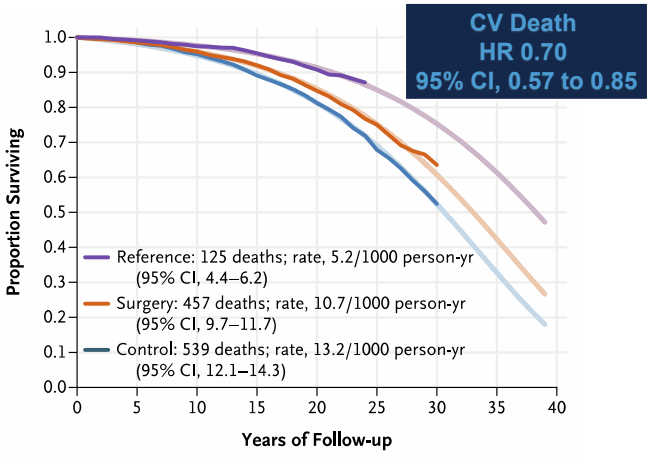
Lean et al. Lancet 2018; 391: 541–51

25

Weight Loss Associated with Lower Rates of Death

n=2,007 Patients Treat with Bariatric Surgery





No. at Risk							
Reference	1135	1125	1106	1083	905	0	0
Surgery	2007	1915	1837	1744	1390	580	34
Control	2040	1961	1815	1589	1238	488	26

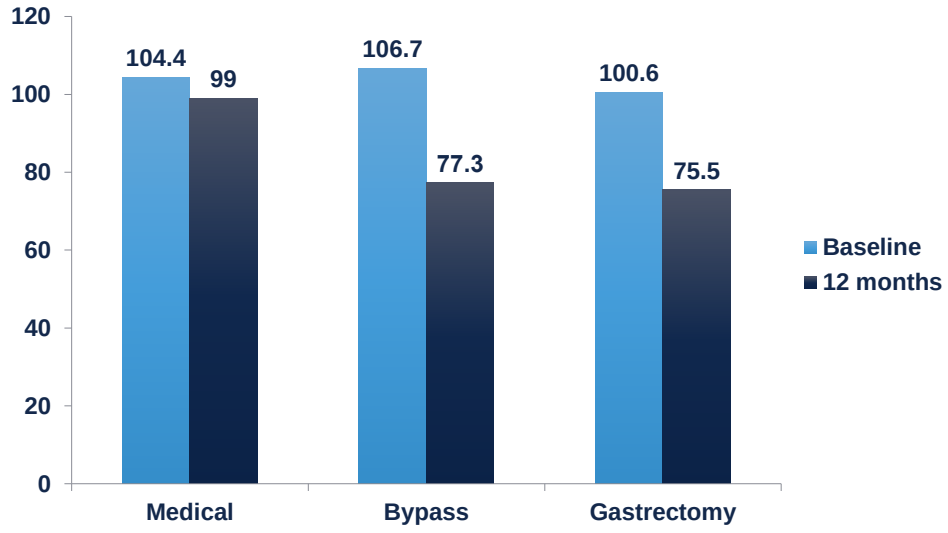
N Engl J Med 2020;383:1535-43

26

Weight Loss with Medical Tx versus Surgery

n=150 Obese Pts with T2DM (STAMPEDE 5 Year Follow-up)

UNC SCHOOL OF MEDICINE



N Engl J Med 2017; 376: 641-51

27

Importance of CV Safety in Obesity

UNC SCHOOL OF MEDICINE

	Look AHEAD[1]	SOS[2]	SCOUT[3]	CRESCENDO[4]	LIGHT[5]	CONVENE[6]	CAMELLIA-TIMI[7]	SELECT[8]	AQCLAIM[9]
Intervention	Lifestyle +/- orlistat	Surgery	Sibutramine*	Rimonabant*	Naltrexone/ bupropion	Naltrexone/ bupropion	Lorcaserin*	Once-weekly semaglutide	Phentermine/ topiramate
Primary outcome	3P-MACE + hospitalisation	Overall mortality	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+	3P-MACE	3P-MACE
Trial status	**Terminated prematurely** *(stopped due to futility)*	**Completed**	**Completed**	**Terminated prematurely** *(safety concerns)*	**Terminated prematurely** *(study integrity compromised)*	**Terminated prematurely** *(selling of US rights)*	**Completed**	**Completed**	**Not started**
Safety / outcome results	Safe / neutral	Safe / benefits (mortality + CV death + first MI or stroke)[2]	Not safe / harm†	Not safe‡ / neutral	Safe / neutral *(integrity compromised)*	No data available	CV safe / harm (cancer)	N/A	N/A

*The following drugs have been withdrawn by the FDA: rimonabant (2008), sibutramine (2010), lorcaserin (2020).
†Increased MACE events with sibutramine vs placebo; ‡increased neuropsychiatric, serious psychiatric and GI effects with rimonabant vs placebo.
3P-MACE, composite of CV death, nonfatal MI and nonfatal stroke; MACE+, composite of myocardial infarction, stroke, CV death and hospitalisation due to unstable angina, heart failure or any coronary revascularisation. CV, cardiovascular; GI, gastrointestinal; MI, myocardial infarction; 3P-MACE, 3-point major adverse cardiovascular event.

1. Look AHEAD Research Group. Control Clin Trials 2003;24:610–28; 2. Sjostrom et al. JAMA 2012;307:56–65; 3. James et al. N Engl J Med 2010;363:905–17; 4. Topol et al. Lancet 2010,376:517–23; 5. Nissen et al. JAMA 2016;315:990–1004; 6. https://clinicaltrials.gov/ct2/show/NCT02638129 (accessed Nov 2020); 7. Bohula et al. NEJM 2018;379:1107-17; 8. https://clinicaltrials.gov/ct2/show/NCT03574597 (accessed Nov 2020); 9. EU clinical trial register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003946-34/GB.

28

FDA Approved GLP-1 Receptor Agonists

UNC SCHOOL OF MEDICINE

Drug	*Year Approved*	*Administration*
Exenatide	2005	SQ Injection
Liraglutide	2010	SQ Injection
Albiglutide	2014	SQ Injection
Dulaglutide	2014	SQ Injection
Lixisenatide	2016	SQ Injection
Semaglutide	2017	SQ Injection
Semaglutide	2019	Oral
Tirzepetide (GLP1RA/GIP)	2022	SQ Injection

29

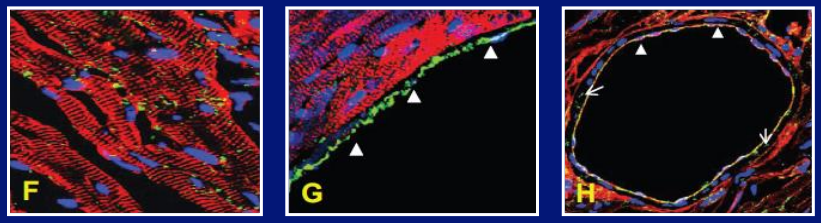
Objectives

UNC SCHOOL OF MEDICINE

- **Review the global prevalence of obesity, diabetes, and CVD and the strong relationship between these conditions**
- **Understand the benefits of current guideline based therapy with a GLP1RA**
- **Discuss common questions and challenges that have prevented more frequent utilization of GLP1RA**

30

rGLP-1 Expression in Mouse Cardiac Tissue



Cardiomyocytes | Endocardial endothelium | Coronary endothelium

- GLP-1 receptors are present in the heart of mice
- GLP-1R protein (IHC) found in coronary arteries of a variety of species
- However, endogenous canonical GLP-1R is not highly expressed in many of the cell types responsive to GLP-1 or GLP-1RA
- Suggests benefit may reflect indirect mechanisms or the actions of ≥1 GLP-1 degradation products acting through GLP-1R-independent mechanisms

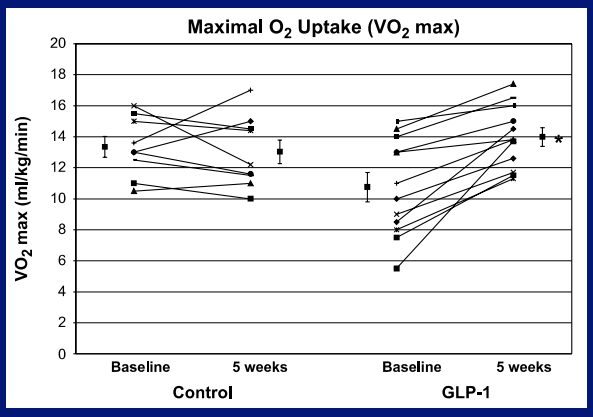
UNC HEALTH CARE

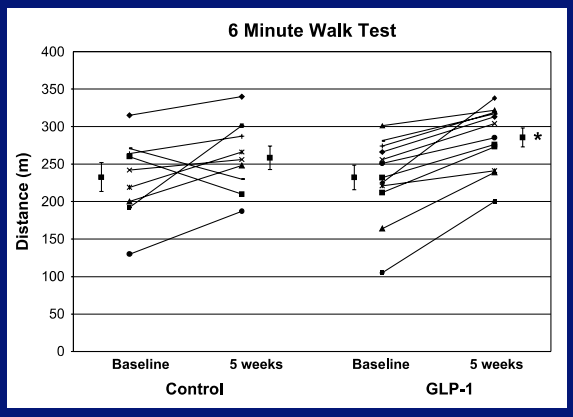
rGLP-1, recombinant GLP.

Ban K, et al. *Circulation*. 2008;117:2340-2350
Kim M, et al. Nat Med. 2013;19:567-575.

31

GLP-1 Infusion Improves LVEF and Functional Status
n= 21 pts w/ CHF





UNC HEALTH CARE

Sokos GG et al. *J Card Fail*. 2006; 12: 694– 699

32

Summary of CV Effects of GLP-1 Receptor Antagonists

UNC SCHOOL OF MEDICINE

	GLP-1 RA n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	NNT (95% CI)	P Value
3-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89-1.17)		0.78
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78-0.97)		0.01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58-0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83-1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68-0.90)		0.0006
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79-0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57-1.11)		0.17
AMPLITUDE-0	189/2717 (7%)	125/1359 (9%)	0.73 (0.58-0.92)		0.0069
Subtotal (I^2 = 44.5%, P = 0.082)			**0.86 (0.80-0.93)**	**65 (45-130)**	**<0.0001**

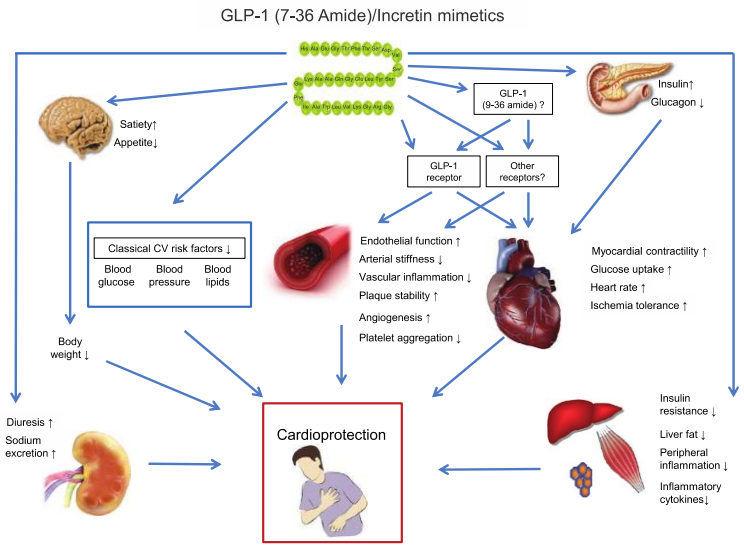
CI, confidence interval; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events.; n, sample size; N, population size; NNT, number needed to treat.
Sattar N, et al. *Lancet Diabetes Endocrinol* 2021;9(10):653–662.

33

Mechanisms of Cardiovascular Benefit in GLP-1RA

n=185 Pts with Obesity After an 8-week Low Carb Diet

UNC SCHOOL OF MEDICINE



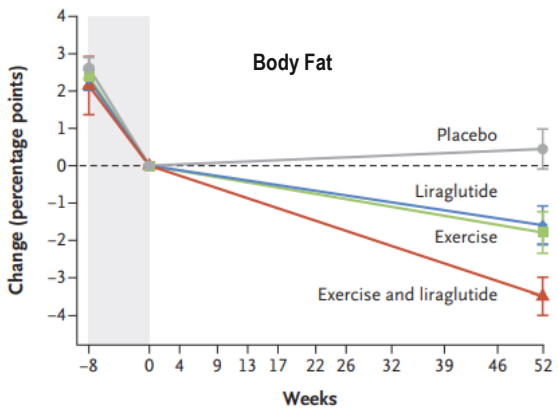
CV, cardiovascular; GLP-1, glucagon-like peptide-1.
Nauck MA, et al. *Circulation* 2017;136:849–870.

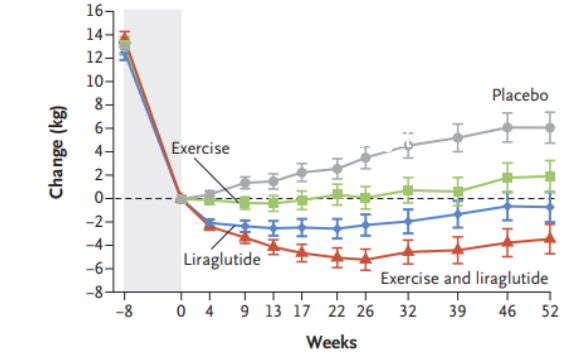
34

Mechanisms of Cardiovascular Benefit in GLP-1RA

n=185 Patients with Obesity After an 8-week Low Carb Diet

UNC SCHOOL OF MEDICINE





No. of Participants 215 195 187 183 181 178 178 175 171 169 168 166

GLP-1 RA, glucagon-like peptide-1 receptor agonist.
Lundgren JR, et al. *NEJM* 2021; 384: 1719–30.

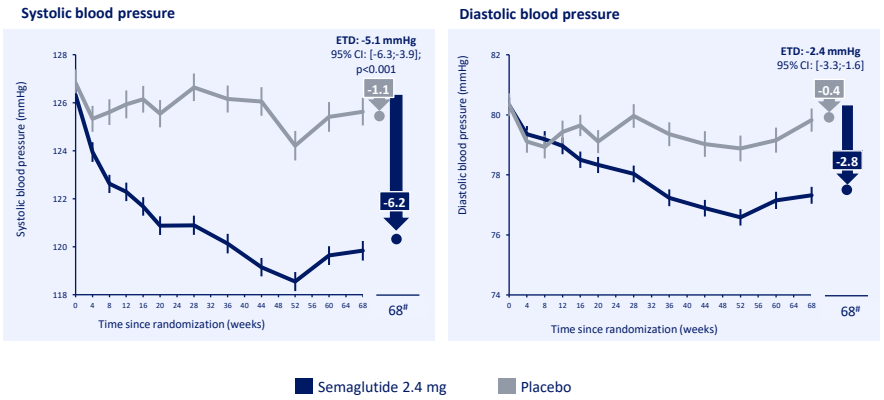
35

Effects on Cardiovascular Risk Factors

UNC SCHOOL OF MEDICINE

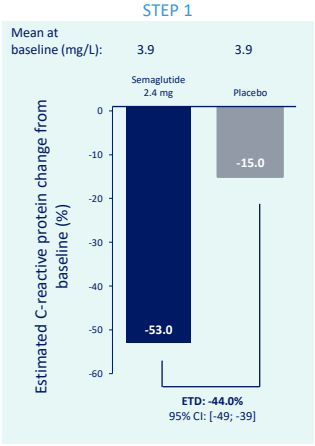
Blood pressure

STEP 1



Inflammation

STEP 1



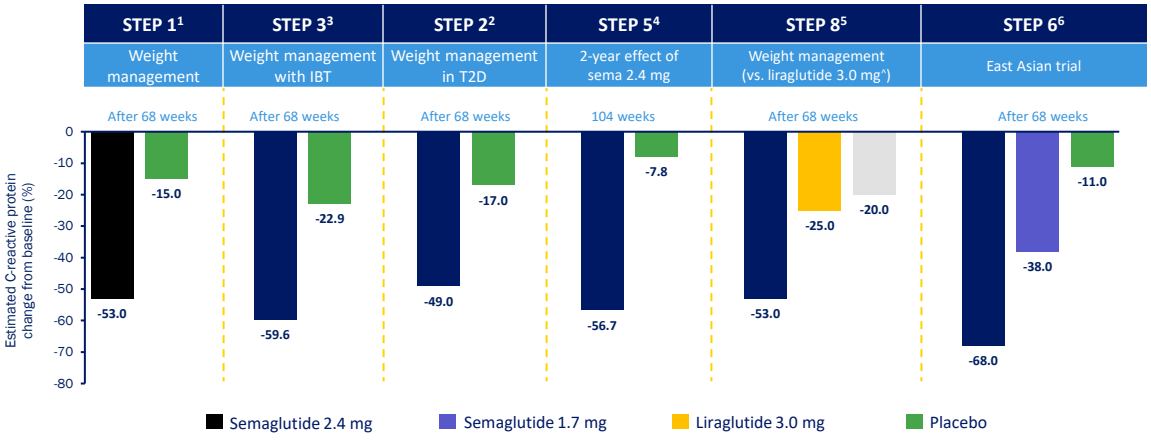
CI, confidence interval; ETD, estimated treatment difference.
Wilding, et al. *N Engl J Med* 2021;384:989–1002; Davies, et al. *Lancet* 2021;397:971–84.

36

Change in C-reactive Protein Across STEP Trials

Semaglutide 2.4 mg Once-weekly in Participants with Overweight or Obesity

UNC SCHOOL OF MEDICINE



Estimated change from baseline for treatment policy estimand.
IBT, intensive behavioural therapy.

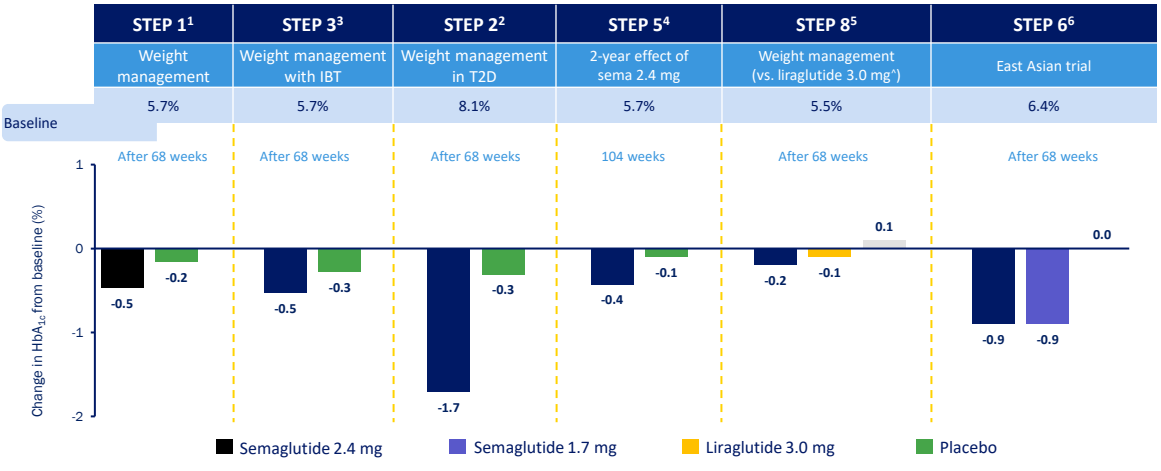
1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 4. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 5. Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 6. Kadowaki et al. Presented at the International Congress on Metabolic Syndrome hybrid meeting .September 2-4, 2021.

37

HbA_{1c} Reduction Across STEP Trials

Semaglutide 2.4 mg Once-weekly in Participants with Overweight or Obesity

UNC SCHOOL OF MEDICINE

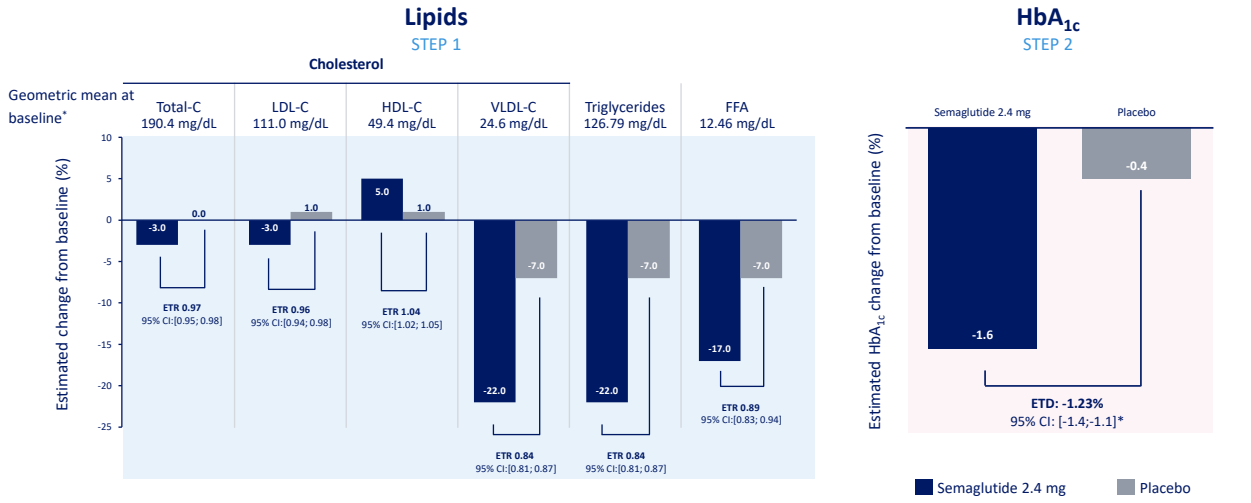


Estimated change from baseline for treatment policy estimand.
HbA1c, glycated haemoglobin; IBT, intensive behavioural therapy.

1. Wilding et al. N Engl J Med 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. Lancet, 2021; doi.org/10.1016/S0140-6736(21)00213-0: 3. Wadden et al. JAMA. doi:10.1001/jama.2021.1831; 4. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 5. Rubino et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021; 6. Kadowaki et al. Presented at the International Congress on Metabolic Syndrome hybrid meeting .September 2-4, 2021.

38

Effects on Cardiometabolic Parameters

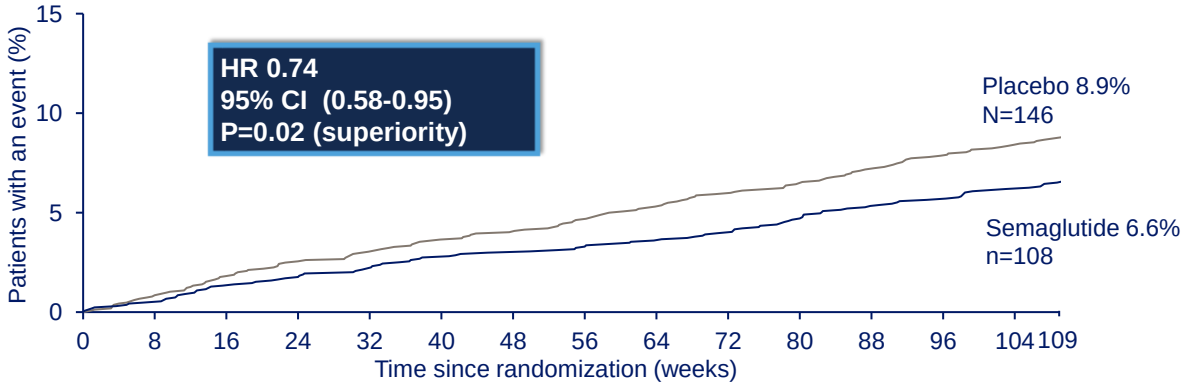


*Geometric mean at baseline for both treatment groups.
C, cholesterol; CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; FFA, free fatty acids; HDL, high-density lipoprotein; LDL; low-density lipoprotein; VLDL, very low-density lipoprotein.
Wilding, et al. *N Engl J Med* 2021;384:989–1002; Davies et al. *Lancet* 2021;397:971–84.

39

SUSTAIN 6 – Semaglutide Reduces CV Events

Time to First Occurrence of CV Death or Non-fatal MI or Non-fatal Stroke



Number of patients at risk

Semaglutide	1648	1619	1601	1584	1568	1543	1524	1513
Placebo	1649	1616	1586	1567	1534	1508	1479	1466

Marso SP et al. *N Engl J Med*. 2016;375:1834.

40

SELECT Trial Design

17,500 patients
- Male or female age ≥45 years
- BMI: ≥27 kg/m^2
- Established CV disease:
  - MI ≥60 days ago
  - Stroke ≥60 days ago
  - Symptomatic PAD
- NYHA IV excluded
- Screening HbA_{1c} <6.5%

Semaglutide 2.4 mg o.w.

Placebo

Event driven

(Estimated duration 54 months, including 7 weeks' follow-up)

Randomisation (1:1)

Trial information
- Superiority trial
- Event driven
- FPFV 24 Oct 2018
- 25 months of recruitment

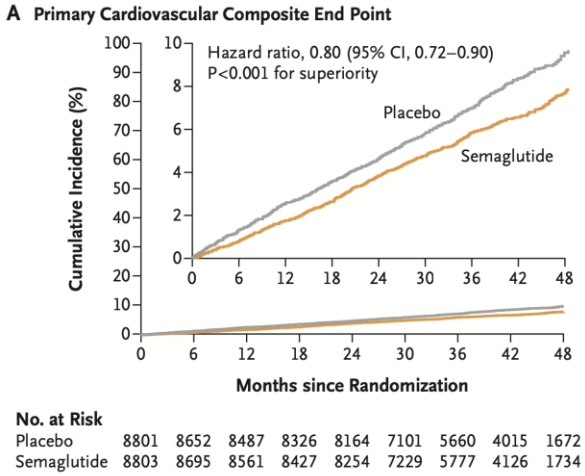
Primary endpoint
- Time from randomisation to first occurrence of MACE (CV death, non-fatal MI, non-fatal stroke)

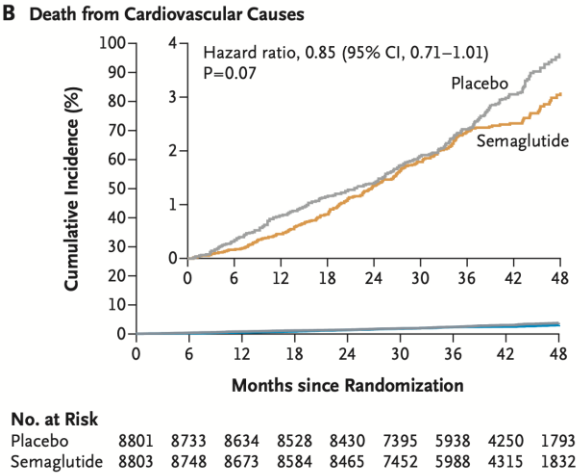
Confirmatory secondary endpoints

Time from randomisation to (first) occurrence of:
- CV death
- All-cause death

41

SELECT Trial Results

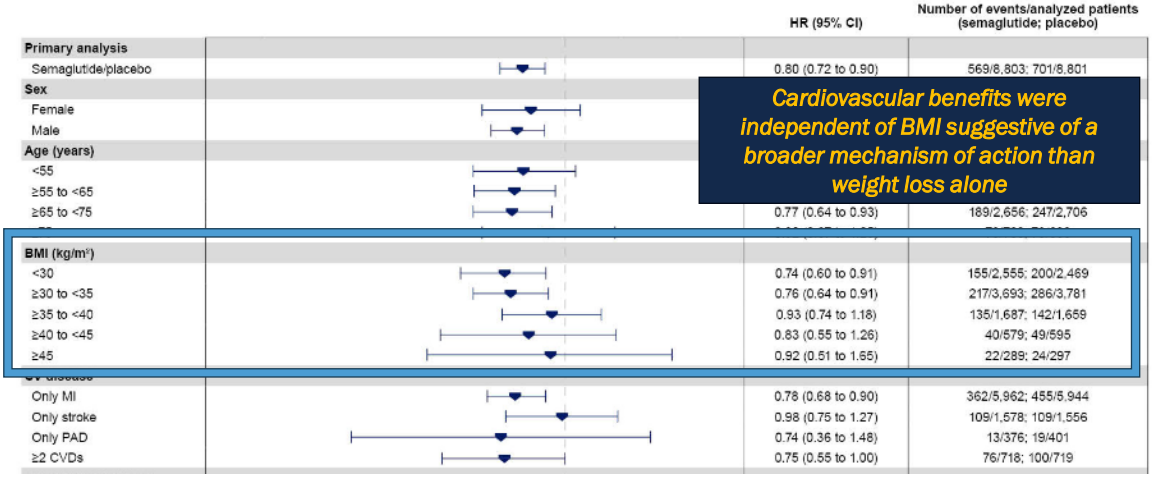




Lincoff AM et al N Engl J Med 2023;389:2221-32

42

SELECT Trial Results



Lincoff AM et al N Engl J Med 2023;389:2221-32

43

SOUL Trial Design

Semaglutide Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes

9,642 patients
- T2D
- Established CVD or CKD
- HbA_{1c} 6.5% - 10%

Oral Semaglutide 14 mg OD + SoC

Placebo + SoC

Duration ~ 3.5-5 years, 1,225 events

Randomization (1:1) — End of treatment

Trial objective
To demonstrate that semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo

Key endpoints
- Primary: Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (MACE)
- Confirmatory secondary:
  - CV death, renal death, onset of persistent ≥ 50% reduction in eGFR, onset of persistent eGFR < 15 mL/min/1.73 m2, initiation of chronic renal replacement therapy (dialysis or kidney transplantation)
  - CV death
  - Major adverse limb events (MALE)

Trial information
- FPFV 17 June 2019 (US)
- FPFV 17 July 2019 (CA)
- FPFV 29 August 2019 (RoW)
- 18/20 month recruitment period
- Double blinded
- Event driven, interim analysis for efficacy
- Sample size: HR 0.83, placebo event rate 3.5%/year
- Superiority trial

Key measurements
- Cognitive function testing
- Bio-banking
- Liver parameters
- Semaglutide Healthcare resource utilisation data

44

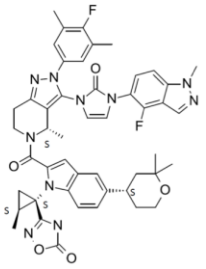
Orforglipron (Oral GLP-1RA)

UNC SCHOOL OF MEDICINE

Orforglipron is a Novel, Once Daily, Non-Peptide GLP-1 Receptor Agonist

- In development as an oral treatment for obesity and T2D in adults.
- It is a partial agonist, biased toward cAMP activation over β-arrestin recruitment at the GLP-1R.
- The half-life of 29 - 49 hours supports once-daily dosing. Oral bioavailability is estimated to be ≈ 30-40 %.
- It can be taken without restriction of food, water, or other medications.

Chemical structure of orforglipron



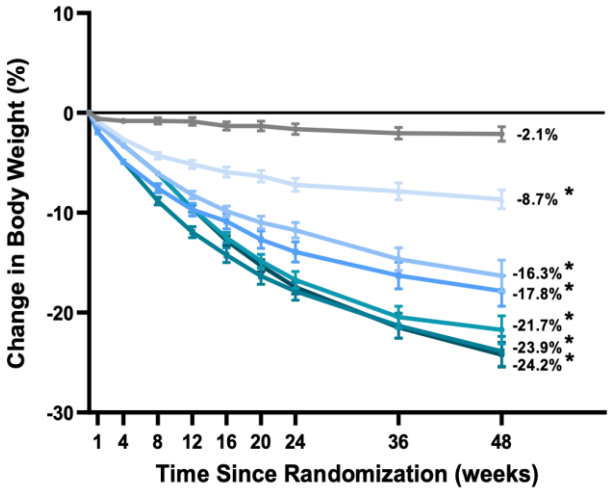
45

Retatrutide in Participants with Obesity without T2D

Triple Agonist (Glucose-dependent Insulinotropic Polypeptide Receptor, GLP-1R, Glucagon Receptor)

UNC SCHOOL OF MEDICINE

Percent Change in Body Weight From Baseline to week 48



Jastreboff AM, et al. *NEJM.* 2

46

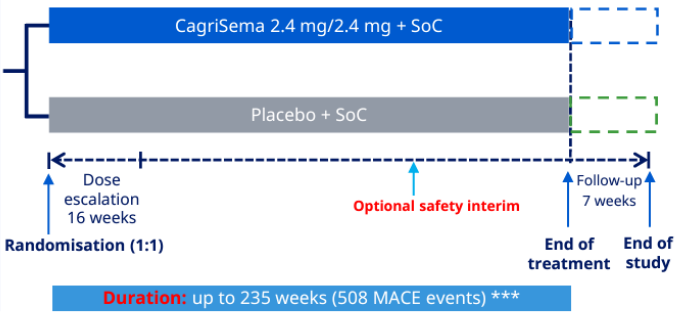
REDEFINE-3 Cardiovascular Outcomes Trial

UNC SCHOOL OF MEDICINE

NN9838-4942

N=7000

- Male or female aged ≥55 years and established CVD*
- BMI: ≥25 kg/m²
- With T2D (80%) or without T2D (20%)
- For participants with T2D:
  - HbA_{1c} 6.5%–10%
  - 0–3 OADs (no GLP-1 RA in last 90 days or during study)
  - Basal insulin permitted
- With or without CKD. Aim for at least 30% with moderate (stage 3) or severe (stage 4) CKD**



Study information

- Randomised, double-blinded, placebo-controlled, non-inferiority study to confirm CV safety of CagriSema
- EMA requests long-term CV safety data as cagrilintide is first in class medicinal product in the EU
- Optional safety interim data for EU submission on WM and EU and FDA submission in T2D
- 235 weeks' treatment duration also allows assessment of neoplasm safety
- Plan for recruitment to be completed in 21 months

Study objective: to confirm **non-inferiority of CagriSema 2.4 mg/2.4 mg versus placebo** with respect to time to first MACE
Study estimand: treatment policy estimand

Key endpoints

Primary endpoint: time to first occurrence of 3-point MACE: CV death, non-fatal MI, non-fatal stroke. Test for non-inferiority and superiority

Secondary endpoint: time to first occurrence of: CV death, composite heart failure endpoint, CKD, all-cause death, expanded MACE, individual components of 3-point MACE, change in body weight, waist circumference, BP, lipids, HbA_{1c}, SF-36, TESAEs, No. of adjudication confirmed malignant neoplasms; No. of severe hypoglycaemic episodes (in participants with T2D at screening), hsCRP, TNF-alpha, IL-6, IL-1 beta, change in pain intensity, sleep quality and neuropathy status

47

SURMOUNT-CVOT
Tirzepatide vs Placebo in Obesity (+/-ASCVD)

UNC SCHOOL OF MEDICINE

Population:
Obesity without diabetes
(BMI 27 kg/m2)
With or without diabetes

N=15,000

Tirzepatide
GLP1-RA/GIP Agonist
(Glucose-dependent Insulinotropic Polypeptide Receptor)

Placebo

Primary Composite Endpoint
- ✓ Death
- ✓ MI
- ✓ Stroke
- ✓ Coronary Revascularization
- ✓ Heart Failure

48

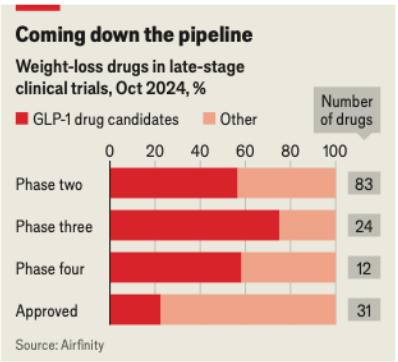
GLP1-RA – An Expanded Indication?

16 The Economist October 26th 2024

Briefing GLP-1 drugs: beyond weight loss

One jab to treat them all

Diabetes, obesity, heart disease, liver and kidney problems—maybe even drug addiction and Alzheimer's. Is there anything GLP-1 drugs cannot treat?



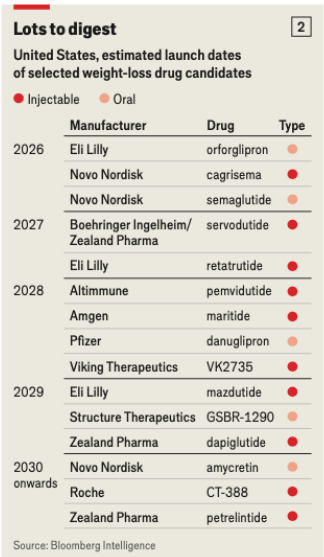
49

GLP1-RA Pipeline

The Economist October 26th 2024

Weight-loss drugs

Pharma frenzy



50

Unanswered Questions - Muscle Loss

VIEWPOINT

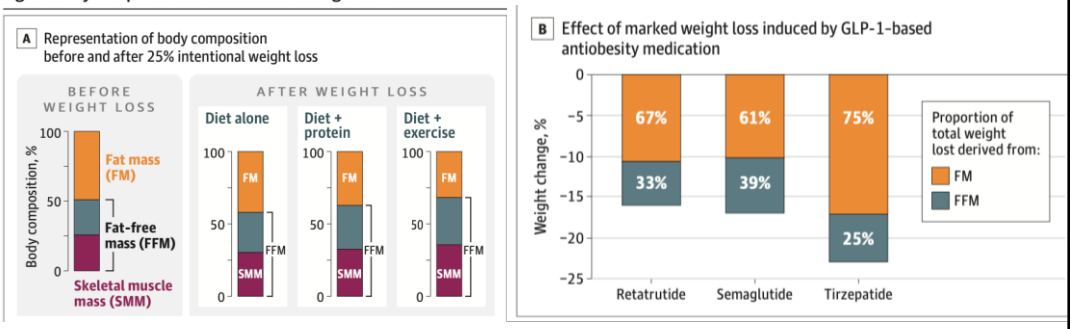
Is Weight Loss–Induced Muscle Mass Loss Clinically Relevant?

Caterina Conte, MD, PhD
San Raffaele Roma Open University, Rome, Italy, and IRCCS MultiMedica, Milan, Italy.

Kevin D. Hall, PhD
National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland.

Samuel Klein, MD
Washington University School of Medicine in St Louis, St Louis, Missouri.

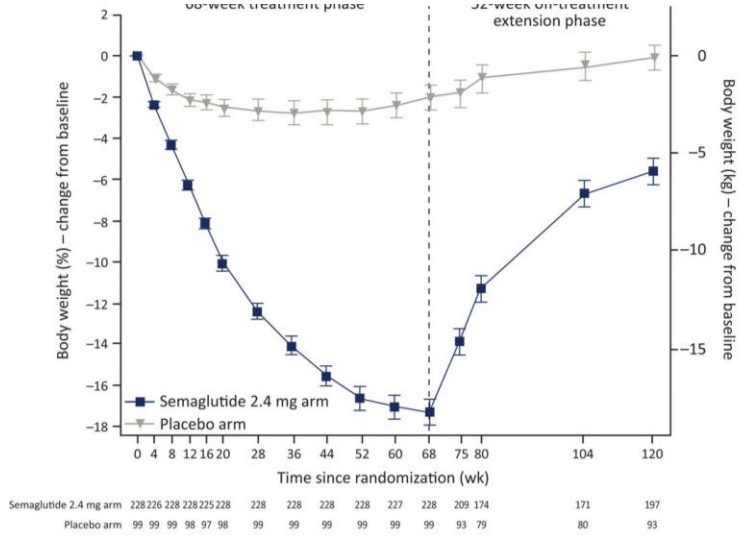
Figure. Body Composition Before and After Weight Loss



JAMA. 2024; 332(1): 9-10

51

Unanswered Questions – Weight Management



Obesity is a lifelong, chronic disease and needs for long-term treatment strategies

Wilding et al. Diabetes Obes Metab. 2022;24:1553

52

What a Cardiologists Needs to Know About GLP-1 Agonist

Mechanism

Increases insulin secretion following food ingestion

Dosing ***(Subcutaneous Administration)***

Liraglutide (0.6mg daily, increase by 0.6mg weekly, max 1.8mg)

Exanatide ER (2mg weekly)

Dulaglutide (0.75mg weekly, increase to 1.5mg weekly)

Semaglutide (0.25 mg weekly. Increase the dose to 0.5 mg after 4 weeks, max 1 mg weekly)

Tirzepatide (2.5 mg weekly, Increase dose by 2.5 mg to max of 15 mg/wk)

ContraIndications

Multiple Endocrine Neoplasia

Side Effects

Increased heart rate, nausea/diarrhea

Administration Notes

Theoretical concern with increased risk of pancreatitis (not shown in clinical studies to date)

UNC HEALTH CARE

Wiernek SL, Cavender MA. *J Fam Pract*. 2017; 66. pii: supp_az_0617

53

What Does AI Have to Say About How to Take a GLP1-RA?

UNC SCHOOL OF MEDICINE

1. ***Follow Your Doctor's Instructions -*** take the medication exactly as prescribed. This includes the dosage, timing, and method of administration
2. ***Monitor for Side Effects -*** Common side effects include nausea, vomiting, diarrhea, and loss of appetite. These often improve over time, but if they persist or become severe, contact your healthcare provider
3. ***Dietary Adjustments -*** Eating smaller, more frequent meals and avoiding high-fat and high-sugar foods can help minimize gastrointestinal side effects
4. ***Stay Hydrated -*** Drink plenty of water, especially if you experience vomiting or diarrhea, to prevent dehydration.
5. ***Be Patient -*** It may take a few weeks to see the full benefits of the medication. Consistency is key, so stick with your treatment plan.
6. ***Monitor Blood Sugar Levels -*** Regularly check your blood sugar levels as advised by your healthcare provider to ensure the medication is working effectively.
7. ***Report Any Unusual Symptoms -*** If you experience symptoms like severe abdominal pain, signs of pancreatitis, or any other unusual symptoms, seek medical attention immediately
8. ***Lifestyle Changes -*** Incorporate healthy eating habits and regular physical activity into your routine to enhance the effectiveness of the medication.

54

Conclusions

UNC SCHOOL OF MEDICINE

- Increasing prevalence of obesity and cardiovascular disease is a major, global healthcare challenge
- Incidence and prevalence of obesity is expected to increase over time
- Obesity and cardiovascular disease are closely related, and obesity is a major risk factor for the development of cardiovascular disease
- Obesity should be considered both a disease and a modifiable risk factor
- Given the availability of drugs with proven cardiovascular benefit for patients with obesity, it is crucial that providers understand how to utilize these therapies