

Treatment of Complicated Patients with Obesity

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Clinic

Disclosures

Company	Disease State/Topic	Role
Novo Nordisk	Obesity	Promotional speaker Advisory board
Acella	Thyroid	Advisory board Promotional speaker
Currax	Obesity	Advisory board Promotional speaker
Lilly	Obesity and Sleep apnea	Advisory Board Promotional speaker
BI	Obesity	Advisory Board
WW	Obesity	Advisory board

- All relevant financial relationships have been mitigated.

Objectives

- ▶ List the current identified complications of obesity
- ▶ Discuss the pathophysiology of obesity and how it causes various complications
- ▶ Review the treatment of obesity and how this effects complications
- ▶ Identify evidence-based guidelines for pharmacologic management of chronic disease of obesity and how the medication impacts the complications

Common Complications that Respond with the Treatment of Obesity

Hypertension

Diabetes Type 2

Dyslipidemia

MASLD

Depression

Hypertension

Case 1 - Caleb

Caleb is a 44-year-old

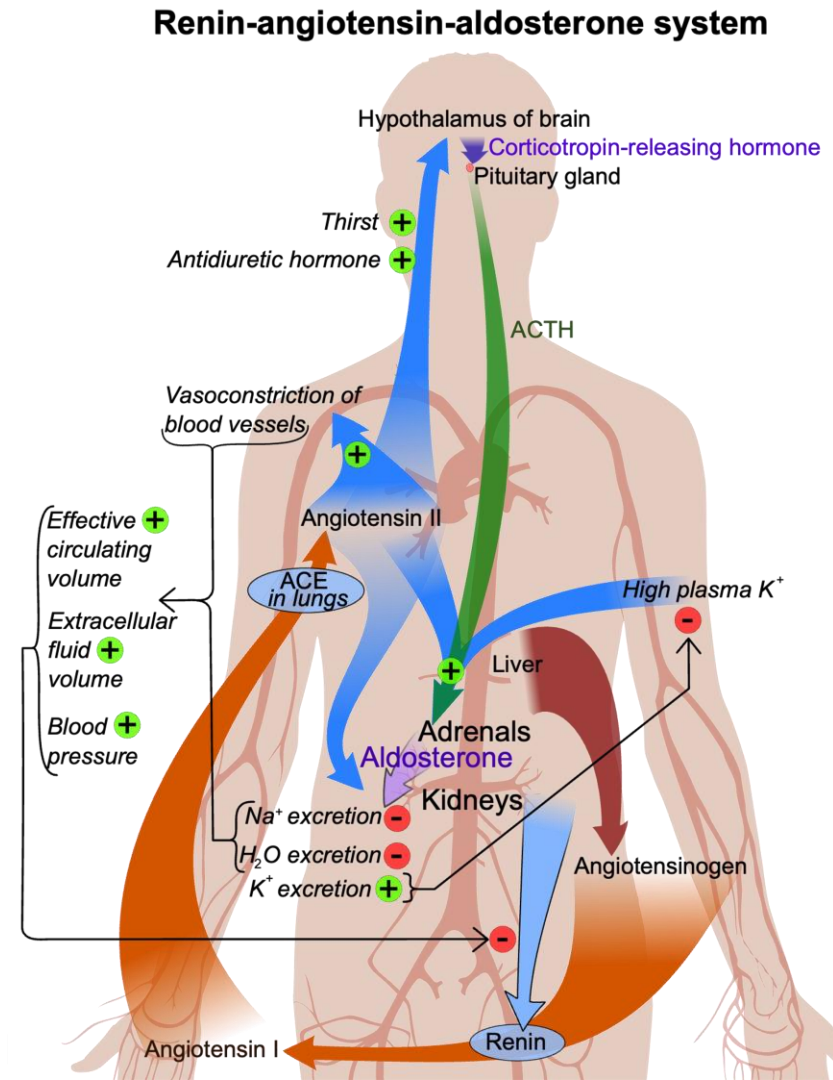
- ▶ PMH: hypertension, dyslipidemia
- ▶ Medication: lisinopril 20mg, rosuvastatin 20 mg
- ▶ VS today
 - ▶ 5'10" 230# BMI 33kg/m²
 - ▶ 128/62 HR 72 RR 16
- ▶ Class 1 (BMI 30-34.9), Stage 2 (Obesity with one or more significant complications)



Photo courtesy of World Obesity Federation

Hypertension

- Obesity connection
 - Increases RAAS = SNS
 - Leptin + inflammation – arterial wall stiffening



Han, T. & Lean, M. *Journal of the Royal Society of Medicine Cardiovascular Disease*, 5, 1-13.

Picture courtesy of By Mikael Häggström - All used images are in public domain.,
Public Domain, <https://commons.wikimedia.org/w/index.php?curid=8458370>

Clinical Implications

- 5-15% weight reduction to achieve BP reduction
 - ▶ AOMS should be considered
 - ▶ orlistat, liraglutide 3mg, semaglutide 2.4mg, tirzepatide 15mg
 - ▶ HR and BP closely with phentermine/topiramate ER
 - ▶ naltrexone ER/bupropion ER not contraindicated as BP is controlled
 - ▶ Bariatric surgery considered: Roux-en-Y or sleeve gastrectomy recommended

Clinical Implications

- Other medications
 - ▶ ACE-I, ARBS first line for HTN if weight loss is not effective with above
 - ▶ Combination therapy add Calcium Channel blocker (beta-blockers and thiazide diuretics may be considered but can have adverse effects on metabolism, beta blockers and alpha blockers promote weight gain)
 - ▶ Aldosterone antagonists for resistant hypertension

Caleb- Treatment plan

► Dietary Options

► James selects Mediterranean eating plan

► PA

► walking 10 minutes after lunch and dinner to work up to 40 minutes a day

► Begins Intensive Lifestyle Intervention program with social worker in practice

► Group meetings every other week

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Photo courtesy of World Obesity Federation

Caleb- Treatment plan

► Medication

► BP controlled with ACE-I

► Shared decision-making: starts phentermine/topiramate

► 7.5mg/46mg until 9 months then increased to 11.25mg/69 mg

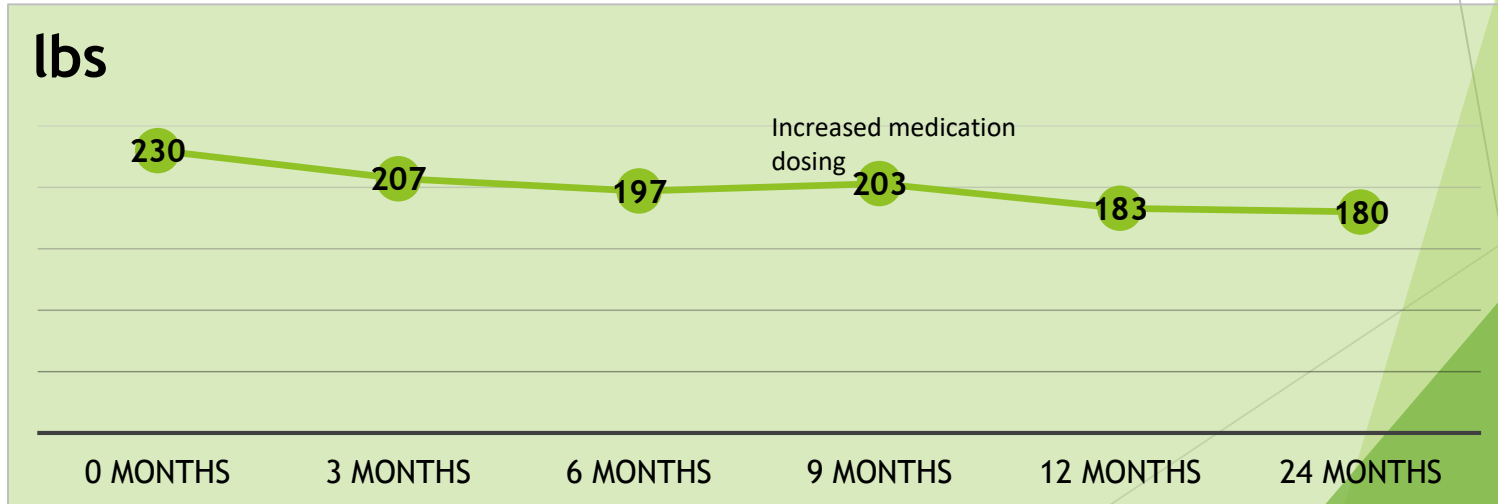


Photo courtesy of World
Obesity Federation



T2DM and ▶ Depression

Sophia

Sophia is a 28-year-old

- ▶ PMH: T2DM (fairly-new diagnosis), depression
- ▶ Medication: metformin 2000 ER every day, citalopram 40 mg every day
- ▶ VS today
 - ▶ 5'6" 225# BMI 36.31kg/m²
 - ▶ 112/62 HR 80 RR 16
 - ▶ PHQ9 11
- ▶ Labs HgBA1C 8.2
- ▶ Class 2 (BMI 35-39.9), Stage 2



Photo courtesy of World Obesity Federation

IR/Prediabetes/DM

► Obesity Connection

- FFAs deposition in muscle, liver and pancreatic beta cells = decreased insulin sensitivity to glucose and insulin resistance
- Leptin from adipocytes – releases aldosterone = Hyperaldosterone leads to further insulin resistance
- Dysfunctional insulin resistant adipocytes redistribute fat to visceral area, more lipid in muscle and hepatocytes

Clinical Implications - Prediabetes

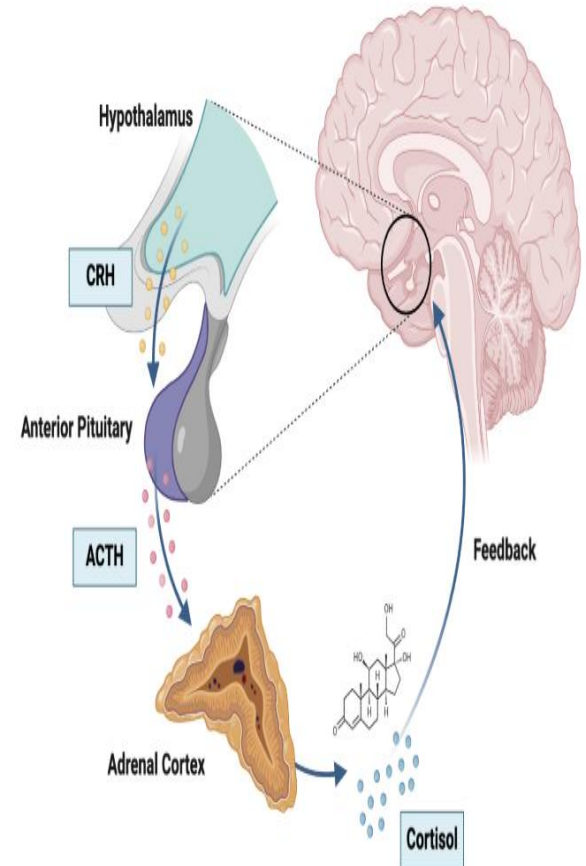
- ▶ 5-15% weight loss OR MORE to achieve lowering of A1C
- ▶ healthy meal plan and physical activity (aerobic and resistance)
- ▶ Consider AOMs
 - ▶ orlistat, phentermine/topiramate ER, liraglutide 3mg, semaglutide 2.4mg, tirzepatide 15mg 10% weight loss
- ▶ Utilize weight neutral or weight loss causing DM meds, if possible
- ▶ Consider referral for bariatric surgery

Psychiatric Implications

- Obesity connection:
 - Systemic inflammation and dysregulation of the HPA axis
 - Social stigmatization with obesity and mental illness
 - Depression is a comorbidity with obesity

Garvey, W., et al. (2016). *Endocrinology Practice*, 22(3), 1-203.
Photo courtesy of Kim, Y. (2025) BioRender.

HPA Axis



Clinical Implications

- ▶ Monitor patients closely for mood disorders and suicidal ideation
- ▶ AACE, 2016:
 - ▶ Obesity Medications
 - ▶ orlistat, liraglutide 3mg, semaglutide 2.4mg and tirzepatide 15mg
 - ▶ naltrexone ER/bupropion ER used with caution or avoided if pt taking an antidepressant
 - ▶ phentermine/topiramate ER - caution with obesity and anxiety and the use of maximal dose
 - ▶ metformin may be beneficial for patients taking antipsychotics
- ▶ Consider use of non obesigenic medications for depression and anxiety

Sophia - Treatment plan

► Dietary Options

► Sophia selects low carbohydrate – well qualified ketogenic eating plan

► PA

► Walking increasing steps to 10,000 a day + Pilates 2 x week

► Begins ILL program

► Group meetings every other week

- PMH: T2DM (fairly-new diagnosis), depression
- Medication: metformin 2000 ER every day, citalopram 40 mg every day
- VS today
 - 5'6" 225# BMI 36.31kg/m²
 - 112/62 HR 80 RR 16
 - PHQ9 11
- Labs HgBA1C 8.2
- Class 2 (BMI 35-39.9), Stage 2



Photo courtesy of World Obesity Federation

Sophia- Treatment plan

► Medication

► Consider changing citalopram d/t possible obesogenic

► More weight neutral: bupropion, fluoxetine, vortioxetine

► Shared decision-making: wants to start semaglutide 2.4mg, prior authorization requests other medications be tried first

► T2DM not controlled – add exenatide, since unable to start sema

► Obesity – add bupropion/naltrexone, stopping citalopram two weeks after starting bupropion

► PMH: T2DM (fairly-new diagnosis), depression

► Medication: metformin 2000 ER every day, citalopram 40 mg every day

► VS today

► 5'6" 225# BMI 36.31kg/m²

► 112/62 HR 80 RR 16

► PHQ9 11

► Labs HgBA1C 8.2

► Class 2 (BMI 35-39.9), Stage 2



Sophia - Treatment plan

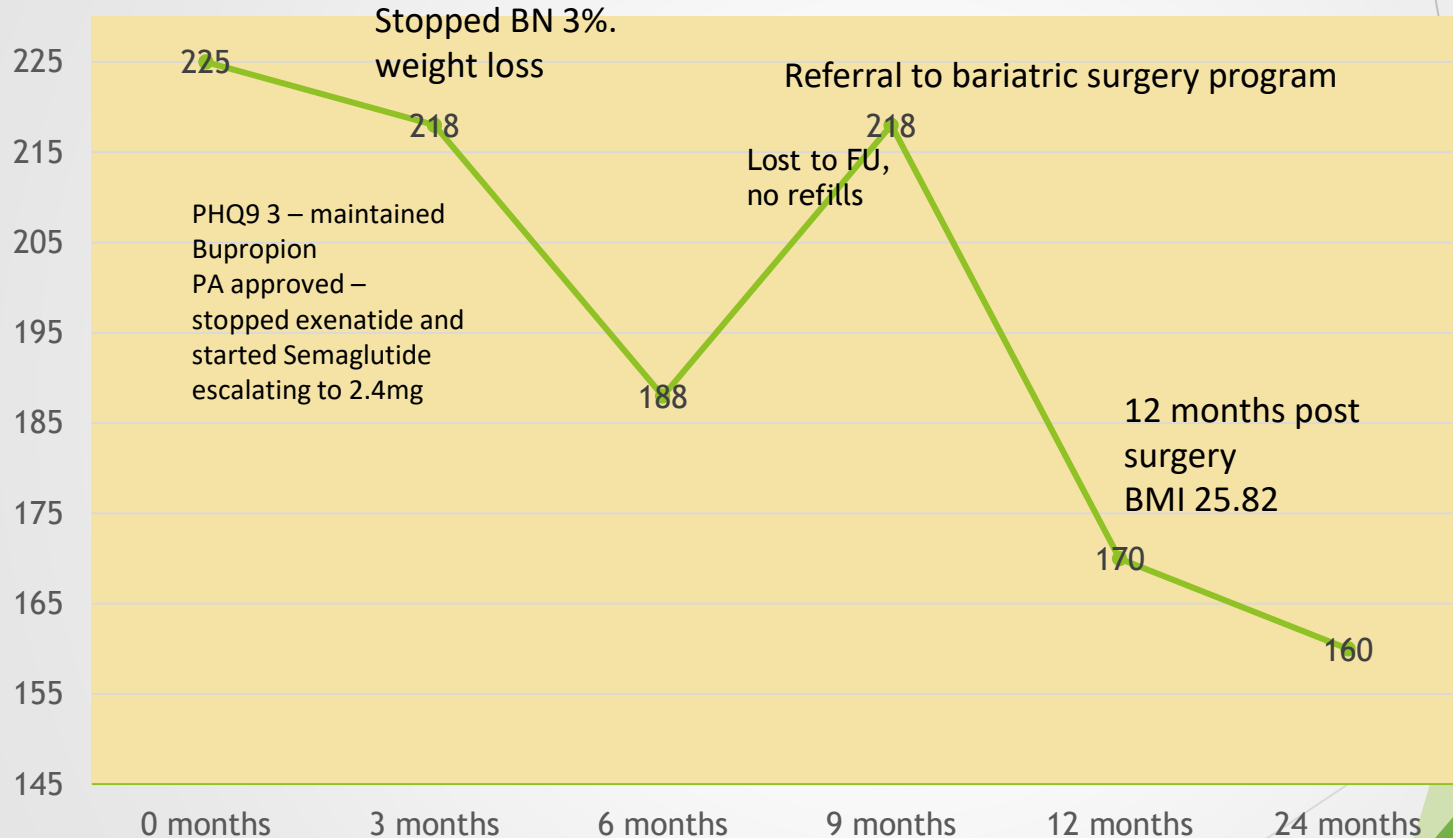


Photo courtesy of World
Obesity Federation

Dyslipidemia and MASLD

Mateo

20-year-old

- ▶ PMH: Dyslipidemia, NAFLD
- ▶ Medication: Algae Omega-3 850mg
- ▶ VS today
 - ▶ 5'11" 222# BMI 30.96 kg/m²
 - ▶ BP 124/86 HR90 RR 20
- ▶ Labs
 - ▶ TC 210mg/dL, LDL 120mg/dL Non-HDL 145 mg/dL, HDL 43mg/dL, Triglycerides 248 mg/dL, CHOL/HDLC ratio 4.2
 - ▶ AST 61 units/L. Alt 72 units/L
 - ▶ Platelet count 219 x 10³/mL
 - ▶ HSI Score 40.4
- ▶ Class 1, Stage 1



Permission to use personal photo

Dyslipidemia

- ▶ Obesity connection:
 - ▶ Insulin resistance also elevates triglycerides
 - ▶ HDL becomes dysfunctional due to the inflammation and oxidative stress
 - ▶ Relationship between BMI and circulating lipids is complex

Clinical Implications

- ▶ 5 to 10% weight loss or more as needed
- ▶ Lifestyle therapy
 - ▶ Physical activity, meal plan minimizing sugar and refined CHO, avoiding trans fats and limit ETOH
 - ▶ PUFAs decrease TG
- ▶ AOMS with life-style therapy
 - ▶ All can be utilized
- ▶ Medications for hyperlipidemia if above unsuccessful

Liver

- ▶ Obesity connection
 - ▶ Visceral adipose tissue produces FFA and diverse inflammatory adipokines
 - ▶ Increases ectopic fat accumulation and inflammation
 - ▶ MASLD (NAFLD) affects 60-80% of patients with DM + obesity and 100% of people with severe obesity

Clinical Implications

- ▶ MASLD treatment is directed at obesity
 - ▶ Lifestyle modifications
 - ▶ 7% weight loss significant improvements in steatosis and lobular inflammation
 - ▶ 9% body weight loss showed histologic improvement (may require as high as 40%)
 - ▶ Bariatric surgery
 - ▶ Some patients experience complete resolution of MASH
 - ▶ Medication: orlistat, liraglutide, semaglutide, tirzepatide



Mateo

Mateo is a 20-year-old

- PMH: Hyperlipidemia, NALFD

- Medication: Algae Omega-3 850mg

- VS today

—5'11" 222# BMI 30.96 kg/m²

—BP 124/86 HR90 RR 20

- Labs

—TC 210mg/dL, LDL 120mg/dL Non-HDL 145 mg/dL, HDL 43mg/dL, Triglycerides 248 mg/dL, CHOL/HDL ratio 4.2

—AST 61 units/L. Alt 72 units/L

—Platelet count 219 x 10³/mL

—HSI Score 40.4

- Class 2, Stage 2

► Dietary Options

- Mateo selects Whole Food Plant Based due to animal rights concern

► PA

- Plays baseball 5 times a week and is in a strength training program

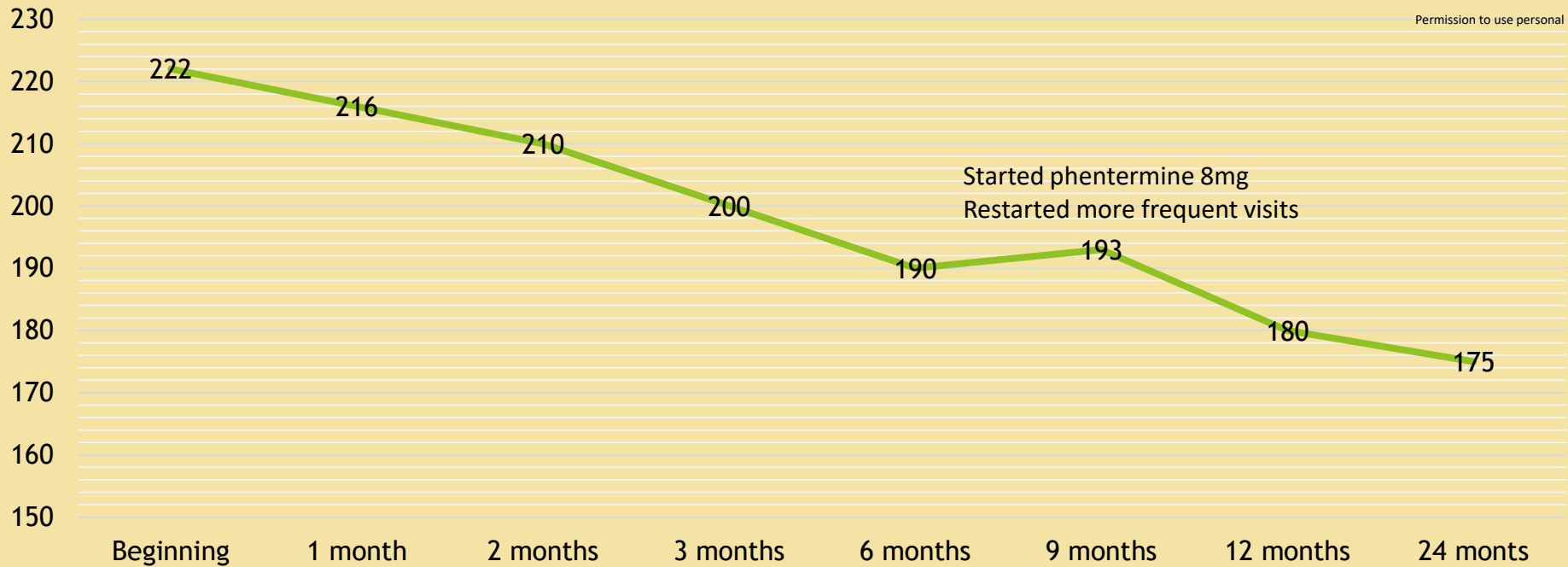
► Begins ILI program

- Individual meetings every other week with provider

Mateo- Treatment plan



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Multiple

- ▶ Complications and Comorbidities

Henry

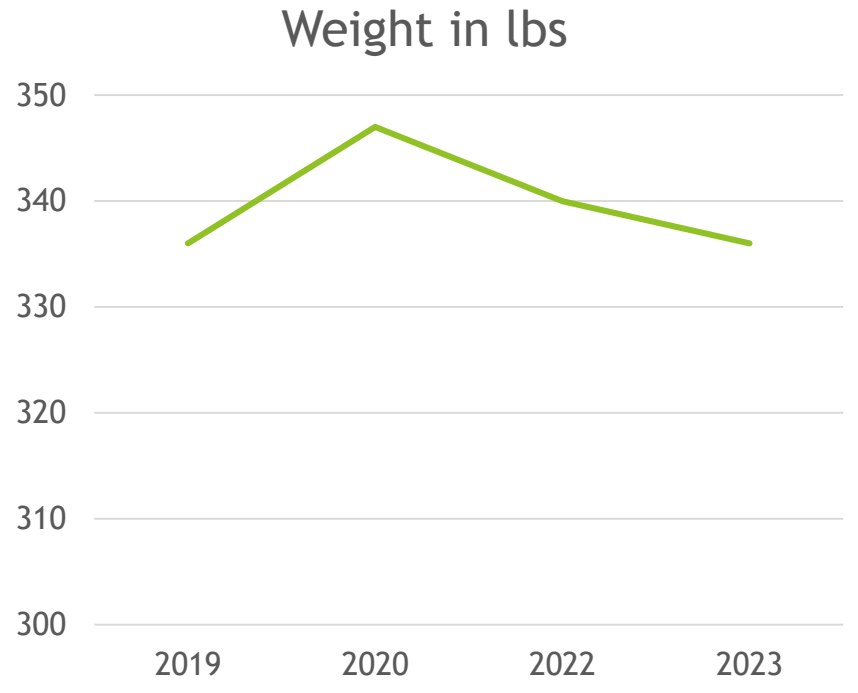
- ▶ Henry is 59-year-old man
- ▶ Diagnosis
 - ▶ Diabetes at age 35 (FH of T2DM in mother and older sister)
 - ▶ Treatment working out at the gym 3-5 times a week
 - ▶ Obesity class 3 (BMI 44)
 - ▶ Hypertension
 - ▶ Mixed dyslipidemia
 - ▶ CAD – MI at age 48
- ▶ CKD Stage 3a
- ▶ Peripheral neuropathy
- ▶ Sleep Apnea
- ▶ MASLD
- ▶ Venous insufficiency



Henry

► Physical exam

- Acanthosis nigricans on neck
- Whitish stretch marks on abdomen
- Bilateral edema on legs
- Reddish brown patches with shiny skin both lower extremities



Henry

▶ Diabetes

- ▶ U-300 insulin glargine 100 unites daily
- ▶ Insulin lispro 4 units with meals + sliding scale
- ▶ Glipizide 10 mg BID
- ▶ Empagliflozin 10 mg QD
 - ▶ Previously on metformin – GI intolerant
 - ▶ Exenatide SQ stopped with insulin

▶ HTN

- ▶ Lisinopril 40mg/d
- ▶ dyslipidemia
 - ▶ rosuvastatin 40 mg qd
- ▶ peripheral neuropathy
 - ▶ gabapentin 600 mg tid

Henry

- ▶ post MI
 - ▶ ACE-I (on for HTN)
 - ▶ Carvedilol 12.5 mg bid
 - ▶ Clopidogrel 75mg/d
 - ▶ Nitroglycerin 0.4mg tablets SL prn
- ▶ venous insufficiency with stasis
 - ▶ compression stockings
 - ▶ tacrolimus ointment 0.1% applied prn for itching
- ▶ CKD
 - ▶ ACE-1 (on for HTN)
 - ▶ Chlorthalidone 25mg qd

Diabetes

- ▶ HgB A1C 9.5%
- ▶ What to do???

Time in Range

Average Blood Glucose 259 mg/dL

Very High >250 mg/dL 55%

High 181 – 250 mg/dL 31%

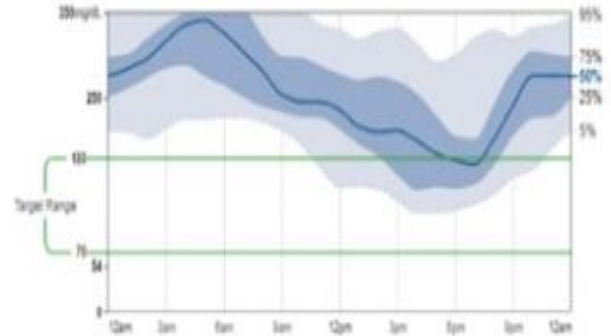
Target range 70 – 180 mg/dL 14%

Low 54 – 69 mg/dL 0%

Very low <54 mg/dL 0%

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%), and other percentiles shown as if occurring in a single day.

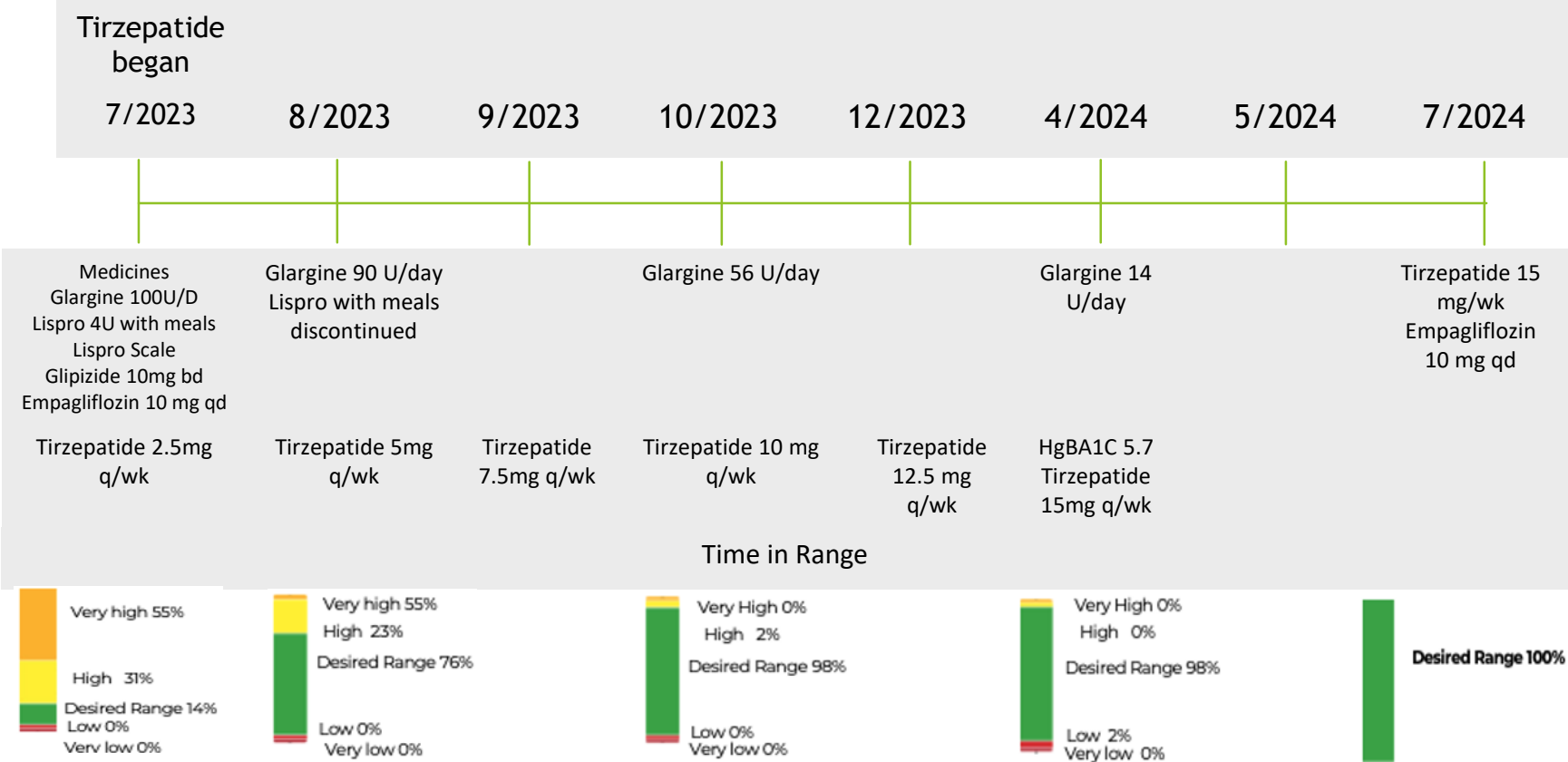


DAILY GLUCOSE PROFILES

Each daily profile represents a midnight-to-midnight period with the data displayed in the upper left corner.



Changes in Treatment and Glucose Levels



Diabetes ADA

Healthy lifestyle behaviors; diabetes self-management education and support; social determinants of health

To avoid therapeutic inertia, reassess and modify treatment regularly (3 to 6 months)

Goal: Cardiorenal risk reduction in high-risk individuals with T2D (in addition to comprehensive CV risk management)*

Goal: Achievement and maintenance of glycemic and weight management goals

+ ASCVD¹

Denied universally across CVOs but all included individuals with established CVD (eg, MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+ Indicators of high risk

While definitions vary, most comprise ≥ 55 years of age with 2 or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+ CKD

eGFR < 60 mL/min per 1.73 m^2 or albuminuria (ACR ≥ 3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+ CKD (on maximally tolerated dose of ACEi/ARB)

+ HF

SGLT2i^o with proven HF benefit in this population

+ ASCVD/indicators of high risk

GLP-1 RA^A with proven CVD benefit **either/or** SGLT2i^o with proven CVD benefit

If A1C above target

- For patient on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD⁵

If additional cardiorenal risk reduction or glycemic lowering needed

Glycemic management: Choose approaches that provide the efficacy to achieve goals:

Metformin or agent(s) including combination therapy that provide adequate efficacy to achieve and maintain treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering

Very high:

Dulaglutide (high dose), semaglutide, tirzepatide
Insulin

Combination oral, combination injectable (GLP-1 RA/insulin)

High:

GLP-1 RA (not listed above), metformin, SGLT2i, sulfonylurea, TZD

Intermediate:

DPP-4i

Achievement and maintenance of weight management goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very high:

Semaglutide, tirzepatide

High:

Dulaglutide, liraglutide

Intermediate:

GLP-1 RA (not listed above), SGLT2i

Neutral:

DPP-4i, metformin

If A1C above target

Identify barriers to goals:

- Consider DSMEs to support self-efficacy in achievement of goals
- Consider technology (eg, diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address social determinants of health that impact achievement of goals

American Diabetes Association. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022; 45:2753.

CKD

Chronic Kidney Disease
EGF < 60 mL/min



Prefer. SGLT2i associated with reduced progression of CKD
Or GLP1RA with CV benefit proven if SGLT2i not tolerated/contraindicated

canagliflozin
dapagliflozin
empagliflozin

semaglutide SQ
dulaglutide
liraglutide

If HgBA1C is above the target, for patients already treated with SGLT2i, consider incorporating GLP1RA

Is Empagliflozin Beneficial in Patients With Variable Chronic Kidney Disease and Diabetes Status?

EMPA-KIDNEY Collaborative Group



6609 patients randomized



2-year follow up



eGFR $\geq 20-45$ ml/min/1.73 m^2
or

eGFR $\geq 45-90$ ml/min/1.73 m^2
and



Urine Albumin to creatinine
ratio of > 200 mg/g

Progressive CKD*
or CV death

Hospitalization for
CHF or CV death

Hospitalization
any cause
(per 100 patient yrs)

Placebo
n=3305



16.9%

4.6%

29.2

HR 0.72 (0.64-0.82)
p< 0.001

HR 0.84 (0.67-1.07)
p=0.15

HR 0.86 (0.78-0.95)
p= 0.003

Empagliflozin
10mg
n=3304



13.1%

4.0%

24.8

*sustained 40% eGFR decline / eGFR < 10 ml/min / ESKD



or



Results were consistent in patients
with and without diabetes

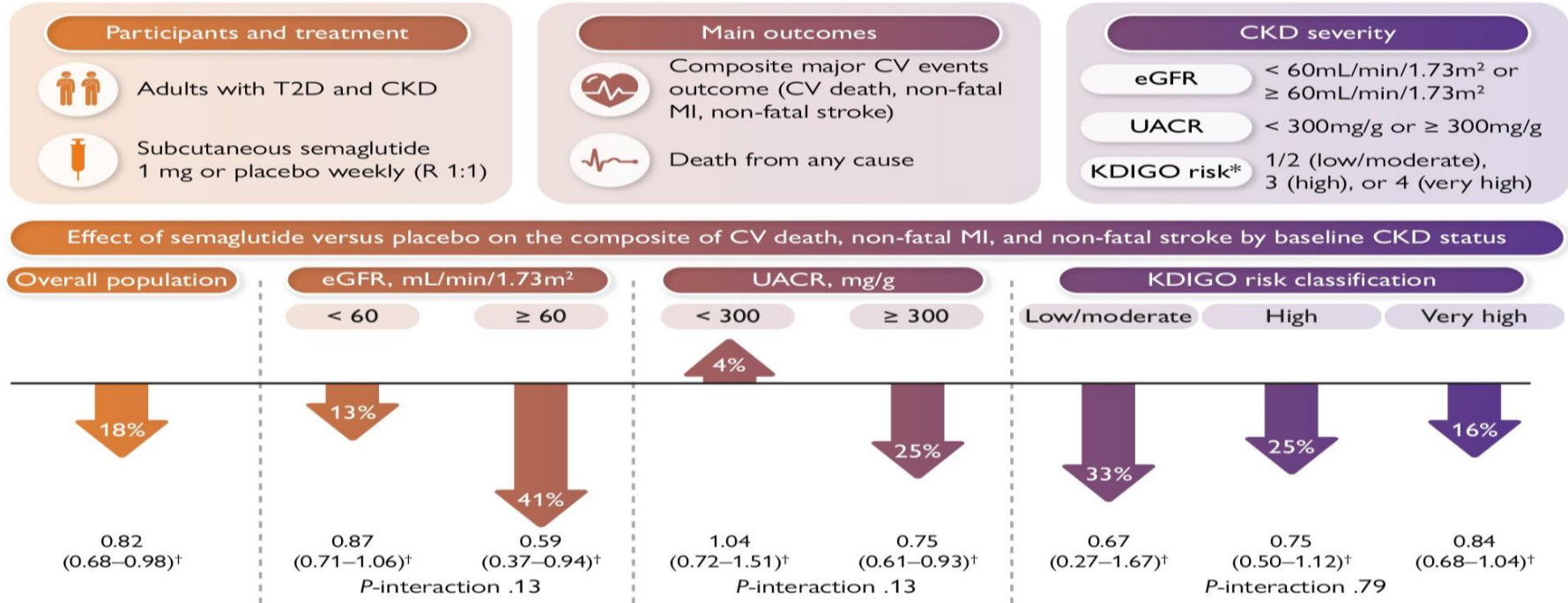
Empagliflozin in Patients with Chronic Kidney Disease: The EMPA-KIDNEY Collaborative Group. Herrington WG, Staplin N, Wanner C, et al. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMoa2204233

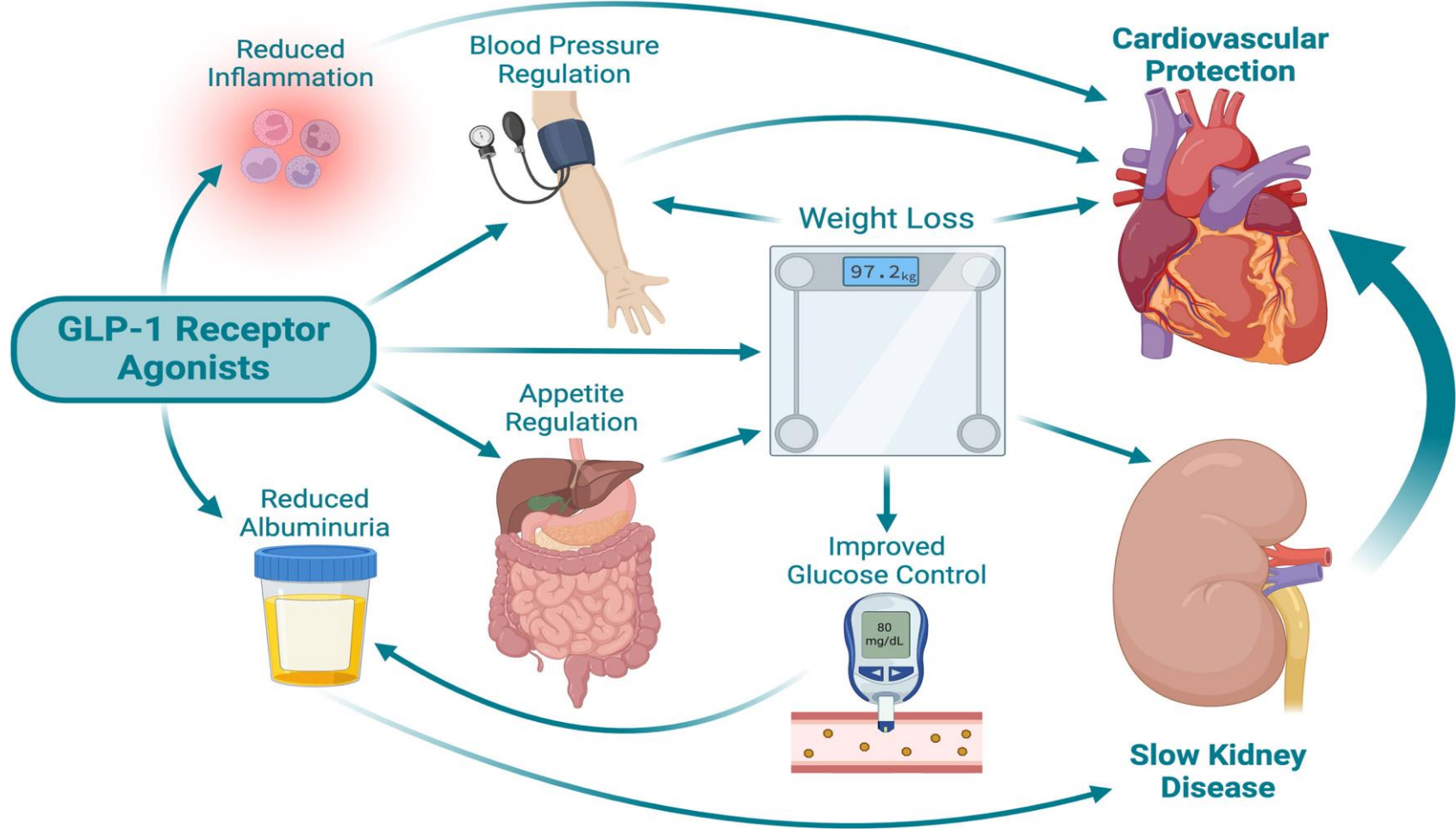
Conclusion: Among a wide range of patients with CKD who were at risk for progression, empagliflozin therapy led to a lower risk of progression of CKD or death from cardiovascular causes than placebo.

@brian_rifkin

FLOW TRIAL

In a prespecified analysis of the FLOW trial, semaglutide 1 mg significantly reduced the risk of CV death/MI/stroke regardless of baseline CKD severity in participants with T2D





Effects of Semaglutide on CKD in Patients With Type 2 Diabetes (2024)

Kotwal, Sradha S. et al. Kidney International Reports, Volume 10, Issue 2, 287 – 290 open access

<https://www.kireports.org/article/S2468-0249%2824%2903387-4/fulltext>

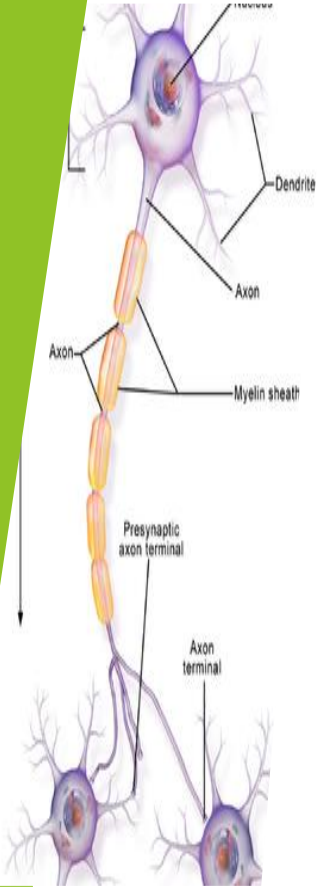
Venous Stasis

- ▶ Treating obesity:
 - ▶ Reduces the overall pressure on the venous system, particularly in the abdomen and lower limbs, improving blood flow
 - ▶ Improves venous flow velocity and reduces vein diameter
 - ▶ lowers incidence of DVT



Photo Courtesy of DermNet

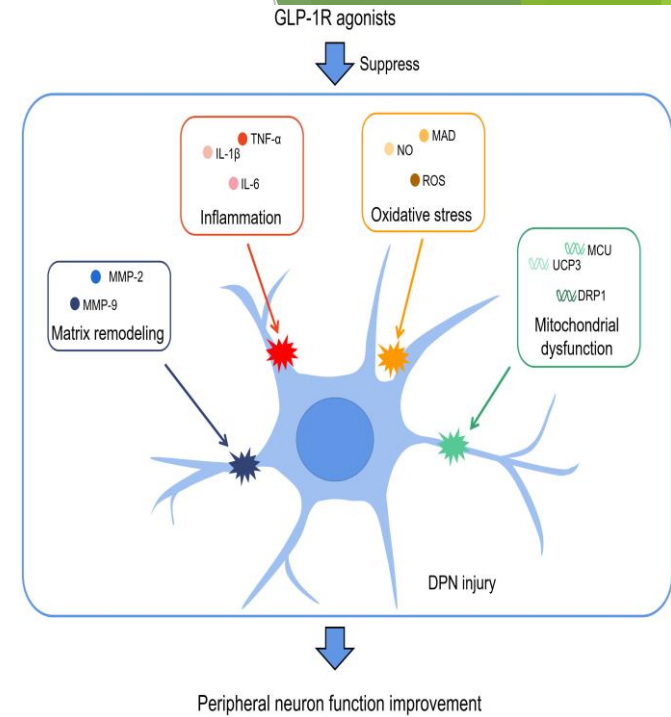
Peripheral Neuropathy



- ▶ characterized by progressive distal-to-proximal axonal degeneration,
- ▶ driven in part by mitochondrial dysfunction in both neurons and axons.
 - ▶ Dysfunctional mitochondria are unable to meet the energy requirements necessary for both axonal maintenance and mitochondrial transport, ultimately impairing axonal health and function at the terminal ends.
- ▶ Studies demonstrate that saturated fatty acids impair peripheral nerves impairing mitochondrial function and bioenergetics, leading to distal axonal loss.

Treatment of PN

- ▶ Dietary interventions
 - ▶ Mediterranean = lower incidence of PN in pts with T1 and T2 DM
 - ▶ Low-fat, plant based w B12 supplementation decreased pain measurements in patients with PN and DM
- ▶ Prospective studies in PN with DM treated with GLP-1RA demonstrated improvements in clinical neuropathy scores, nerve conduction studies, and axonal excitability recordings.

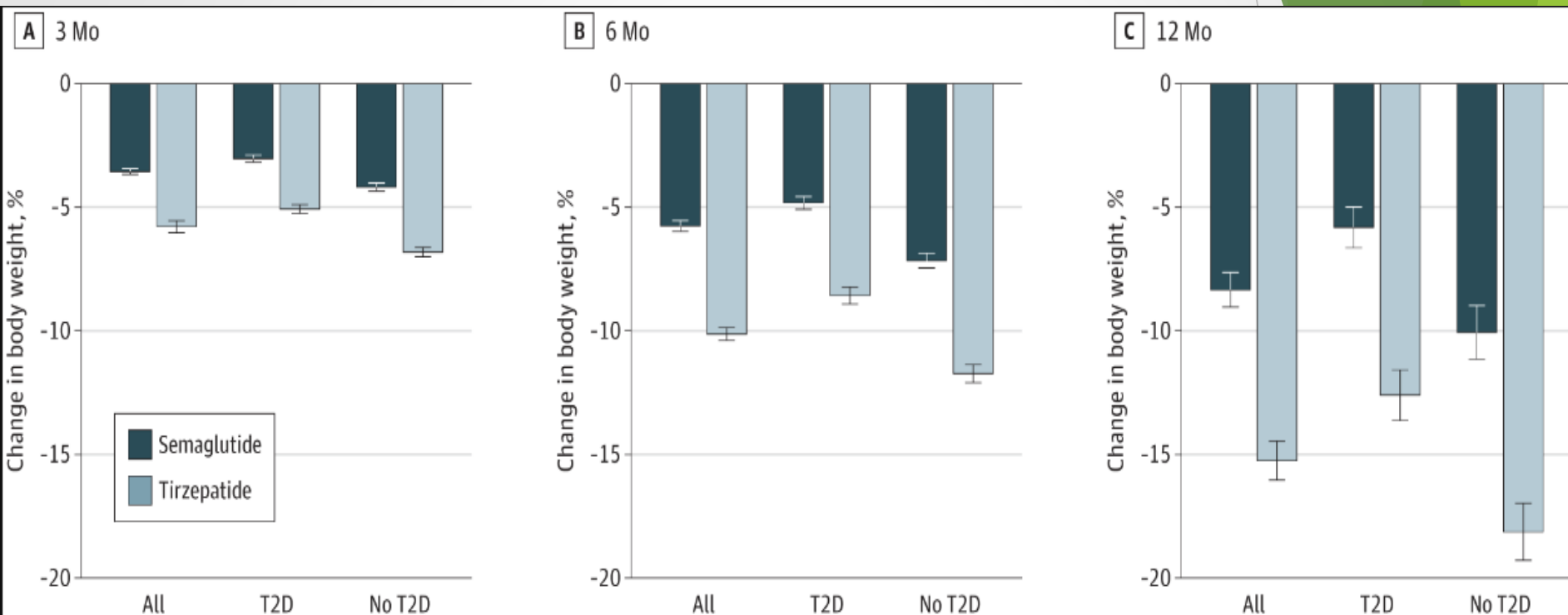


Dhanapalaratnam, R., Issar, T., Poynten, A. M., Milner, K. L., Kwai, N. C. G., & Krishnan, A. V. (2025). Impact of glucagon-like peptide-1 receptor agonists on axonal function in diabetic peripheral neuropathy. *Journal of neurophysiology*, 133(1), 14–21. <https://doi.org/10.1152/jn.00228.2024>

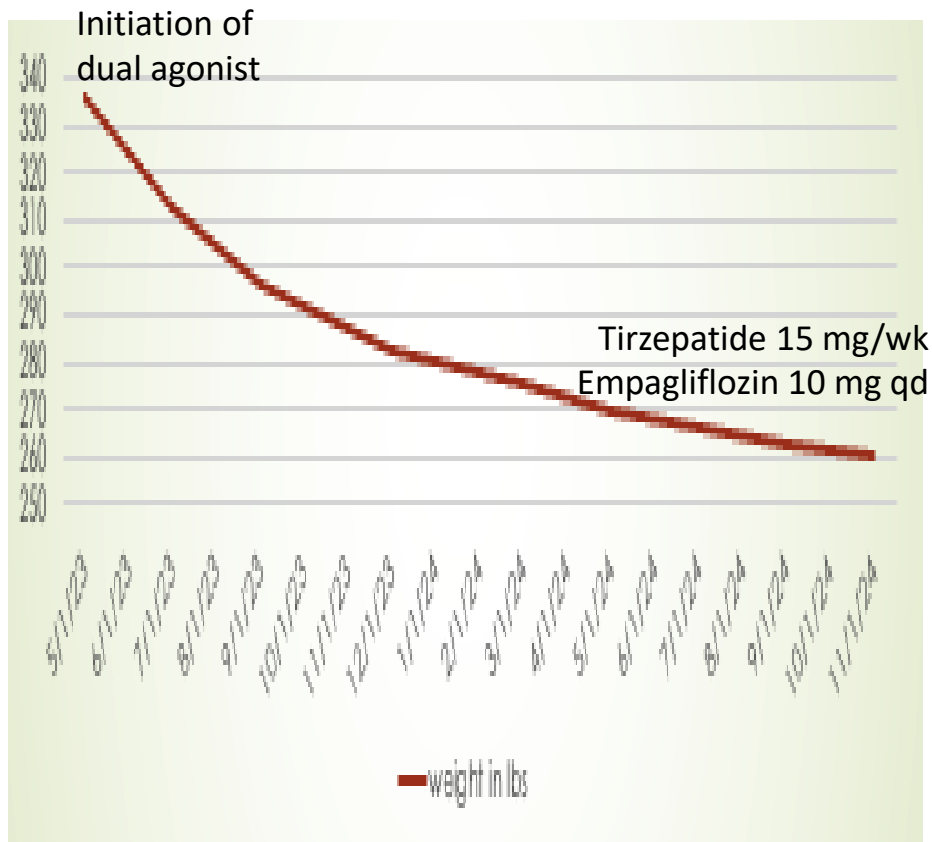
Liu, C., Wu, T., & Ren, N. (2024). Glucagon-like peptide-1 receptor agonists for the management of diabetic peripheral neuropathy. *Frontiers in endocrinology*, 14, 1268619. <https://doi.org/10.3389/fendo.2023.1268619>

<https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2023.1268619/full> open access

Weight Loss with GLP-1 RA/GLP1-RA GIP



Weight Graph



- ▶ Diabetes
 - ▶ Tirzepatide 15mg/wk
 - ▶ Empagliflozin 10 mg QD
- ▶ HTN
 - ▶ resolved
- ▶ dyslipidemia
 - ▶ resolved
- ▶ peripheral neuropathy
 - ▶ D/C gabapentin
- ▶ post MI
 - ▶ Lisinopril 40mg/d
 - ▶ Carvedilol 12.5 mg bid
 - ▶ Clopidogrel 75mg/d
 - ▶ Nitroglycerin 0.4mg tablets SL prn
- ▶ venous insufficiency with stasis
 - ▶ compression stockings
- ▶ CKD
 - ▶ ACE-1 (on for post MI)
 - ▶ Chlorthalidone 25mg qd

Helen

- ▶ A 79-year-old
- ▶ PMH
 - ▶ Hypertension: lisinopril 10 mg daily
 - ▶ Obesity: DASH diet prescribed by cardiology
 - ▶ type 2 diabetes: sitagliptin 50mg qd
- ▶ HPI
 - ▶ shortness of breath on exertion, worsened over the past six months.
 - ▶ denies chest pain but reports difficulty carrying groceries and other daily activities.
- ▶ PE: BP 168/98, HR 94 at rest, non-pitting peripheral edema, jugular venous distention
- ▶ Diagnostics:
 - ▶ echocardiogram shows mild left ventricular hypertrophy with an EF of 55%.
- ▶ Findings suggest Heart Failure with preserved Ejection Fraction.



Studies

► DELIVER

- Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction.

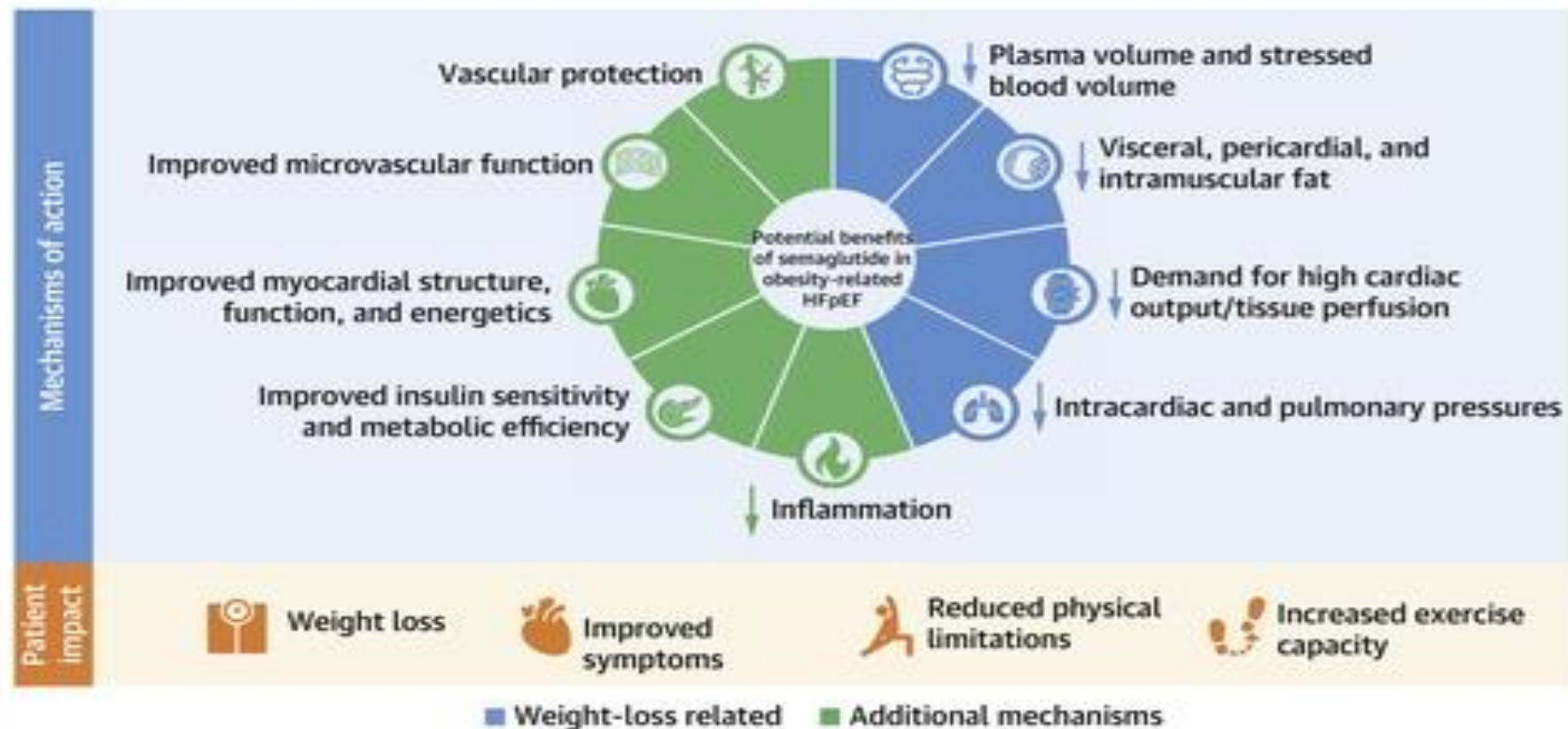
► EMPEROR-Preserved

- Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.

► STEP-HFpEF and STEP-HFpEF DM

- Semaglutide
- most participants received diuretic agents and renin-angiotensin blockers at baseline, and approximately
- one-third were on mineralocorticoid receptor antagonists
- Sodium-glucose cotransporter-2 inhibitor use was rare in STEP-HFpEF but not in STEP HFpEF DM (32%)
- Conclusions: Patients in both trials had marked symptomatic and functional impairments

CENTRAL ILLUSTRATION: Potential Mechanisms of Benefit for Semaglutide in Individuals With the Obesity Phenotype of HFpEF





Ryan, D. H., et al. (2020). Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *American heart journal*, 229, 61–69. <https://doi.org/10.1016/j.ahj.2020.07.008> open access

Treatment Approaches

- ▶ Lifestyle Modifications:
 - ▶ Weight loss, sodium restriction, and exercise training are crucial.
- ▶ Medications:
 - ▶ Hydrochlorothiazide 25mg added
- ▶ Specific Therapies:
 - ▶ Stop sitagliptin and consider SGLT2I (dapagliflozin or empagliflozin) or GLP1 (semaglutide)



Key Take Aways



Obesity is a chronic and often progressive, but treatable disease

Obesity management is part of a comprehensive plan with other diseases

Intervention means impacting all the diseases a patient may have, aware of obesogenic medications



Thank you
▶ Q and A

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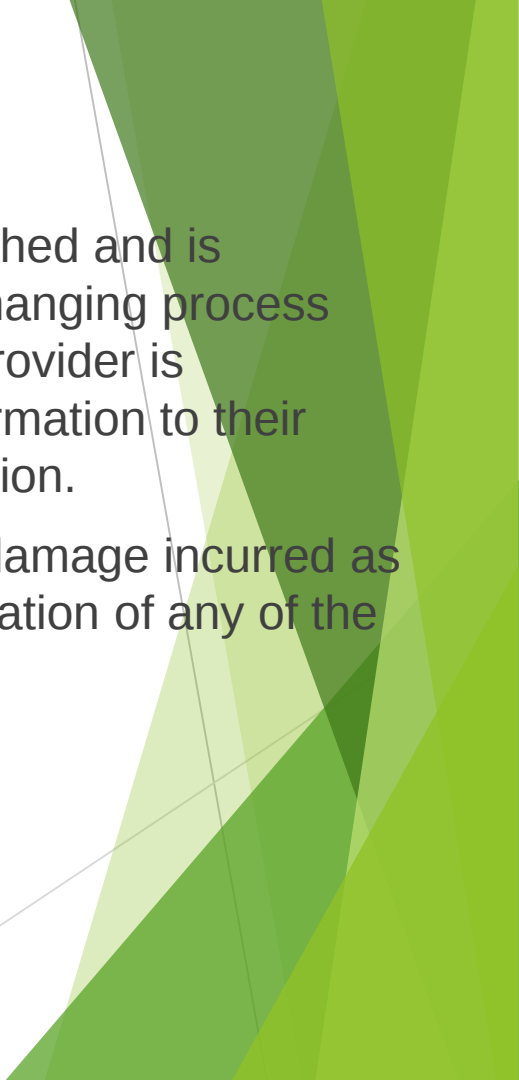
twitter: @DrAngieNP

IG: npobesitytreatment

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