West Virginia University
School of Pharmacy

Other Duties As Assigned:

Incretin Therapy Uses Outside Diabetes

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Faculty Disclosure

I have nothing to disclose concerning possible financial relationships with ineligible companies that may have a direct or indirect interest in the subject matter of this presentation.

I will be discussing off-label uses of certain medications during this presentation.

Objectives

- Comparatively review data underlying FDA-approved indications for incretin-based therapies beyond Type 2 diabetes
- Summarize clinical trial data that may support future indications for current incretin-based therapies
- Review data for investigational incretin-based combination therapies beyond Type 2 diabetes

Question 1

- The incretin effect was first clearly demonstrated in the:
  - 1930s
  - 1960s
  - 1980s
  - 2000s

Question 2

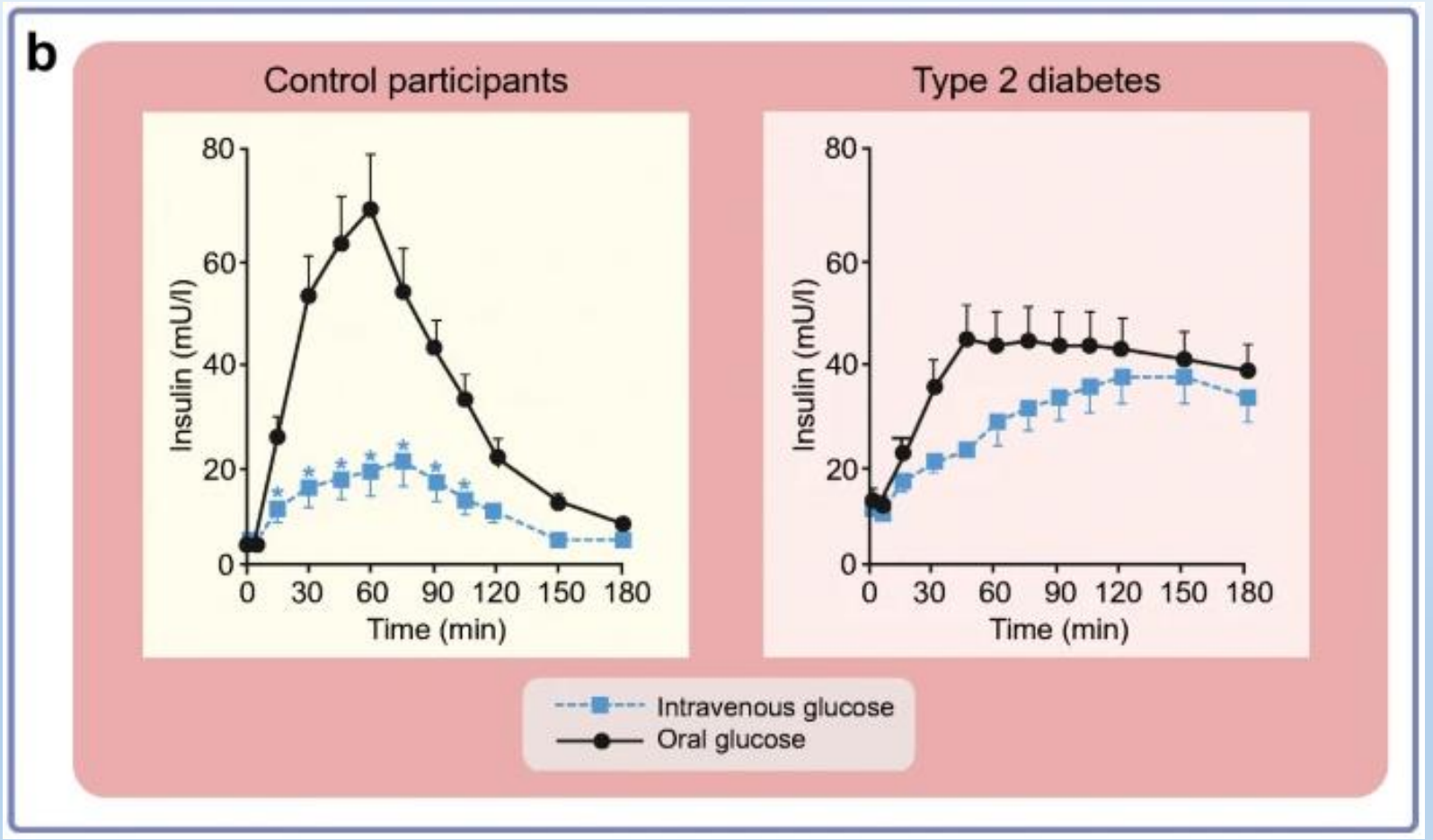
- In healthy adults, which of the following hormones has the greatest potency as an incretin?
  - GIP
  - GLP-1
  - GLP-2
  - Amylin

Incretin History

- In early 1900s, it was noted that extracts from the intestine could lower urinary glucose in patients with diabetes, leading to an inference of factors derived there
- In the 1960s, it was noted that insulin levels rose more when glucose was delivered orally than when given intravenously
  - Labelled the incretin effect

Novikoff & Muller, Physiology 2024: 39; 142-56

Incretin Effect



Drucker & Holst, Diabetalogia 2023: 66; 1765-79

Incretins

- GIP (glucose-dependent insulinotropic polypeptide)
  - Isolated in early 1970s, and demonstrated potent incretin effectiveness
  - Later shown to be largely ineffective in patients with diabetes

- GLP-1 (glucagon-like peptide 1)
  - Identified in late 1980s as a product of differential cleavage of the proglucagon peptide
  - While less potent as an incretin, its activity was retained in patients with diabetes

Drucker & Holst, Diabetalogia 2023: 66; 1765-79

Comparison (Pancreatic Effects)

GIP

- Secreted from K cells in proximal small intestine only in response to food
- Stimulates insulin when glucose is normal or high
- Stimulates glucagon secretion when glucose is normal or low

GLP-1

- Secreted from L cells in distal small intestine only in response to food
- Stimulates insulin when glucose is normal or high
- Inhibits glucagon secretion when glucose is normal or high

Nauk, et al. Diabetes Obes Metab 2021: 23(Suppl 3); 5-29

Extra-pancreatic Comparison

GIP

- Does not alter gastric motility
- Does not induce satiety through central nervous system activation at physiologic levels
- In the presence of insulin, promotes fatty acid uptake and deposition in adipose tissue

GLP-1

- Slows gastric motility (afferent vagus stimulation?)
- Does induce satiety through central nervous system activation (indirect, direct?)
- May indirectly increase fatty acid oxidation through augmentation of sympathetic output

Incretin-Based Therapies

Question 3

- Which of the following has the LEAST effect on GIP receptor binding?
  - Sitagliptin
  - Dulaglutide
  - Tirzepatide
  - None have an impact

DPP4 Inhibitor Mechanism of Action

- DPP4 rapidly breaks down both GIP and GLP-1
  - GIP half-life – 3-4 minutes
  - GLP-1 half-life – 1-2 minutes
- Inhibition of DPP4 roughly doubles the half-life, but that is still short as renal clearance of the incretins is unaffected

- DPP4 inhibitors modestly increase incretin levels in the short term, but they remain in or near the physiologic range
  - Possible anti-inflammatory effects??

GLP-1 Receptor Agonist Mechanism of Action

- Are all derivatives of either exendin-4 or human GLP-1
- Bind to GLP-1 receptors equivalently, but have markedly longer half-lives than endogenous GLP-1
  - Ranges from 2-3 hours to roughly one week
- Achieves supraphysiologic circulating levels that exaggerate the physiologic responses

Tirzepatide Mechanism of Action

- A co-agonist at both the GIP and GLP-1 receptors
- Derived from human GIP, with additional modifications to add GLP-1 receptor binding and markedly slowed DPP4 breakdown
  - Formally, binds GIP receptor with much higher affinity than GLP-1 receptor in *in vitro* studies
  - However, does not stimulate GLP-1 receptor internalization and breakdown, so GLP-1 effect is quite pronounced
- Ultimately, the contributions of each receptor remains unclear

Novikoff & Muller, Physiology 2024: 39; 142-56

Obesity

Question 4

- Which of the following yielded the largest average percent body weight reduction in clinical trials of obese patients?
  - Linagliptin
  - Exenatide ER
  - Liraglutide
  - Tirzepatide

Question 5

- Tachyphylaxis generally develops to all of the following GLP-1 RA effects EXCEPT:
  - Nausea
  - Delayed gastric emptying
  - Weight loss
  - None of the above

DPP4 Inhibitor Weight Loss in DM trials

- Sitagliptin (24 weeks)
  - -0.6 kg
- Saxagliptin (24 weeks)
  - -1.1 kg
- Linagliptin (24 weeks)
  - -0.4 kg
- Alogliptin (26 weeks)
  - +0.68 kg

Aschner, et al. Diabetes Obes Metab 2010; 12: 252-61, Jadzinski, et al. Diabetes Obes Metab 2009; 11: 611-22
Taskinen, et al. Diabetes Obes Metab 2011; 13: 65-74, Pratley, et al. Diabetes Obes Metab 2009; 11: 167-76

GLP-1 RA Weight Loss in DM Trials

- Exenatide IR – -3.1 kg @ 24 weeks
- Exenatide ER – -2.3 kg @ 24 weeks
- *Lixisenatide – -2.0 kg @ 24 weeks
- Liraglutide – -3.5 kg @ 26 weeks
- *Albiglutide – -0.86 kg@ 52 weeks
- Dulaglutide – -2.3 kg @ 26 weeks
- Semaglutide SC – -4.5 kg @ 30 weeks
- Semaglutide PO – -4.4 kg @ 26 weeks

Moretto, et al. Clin Ther 2008:30;1448-60, Blevins, et al. JCEM 2011:96;1301-10, Ahren, et al. Diabetes Care 2013;36:2543-50, Ahmann, et al. Diabetes Obes Metab 2015;17:1056-64, Nauck, et al. Diabetologia 2016;59:266-74, Umpierrez, et al. Diabetes Care 2014;37:2168-76, Sorli, et al. Lancet Diab Endo 2017;5:251-260, Pratley, et al. Lancet 2019;394:39-50

Incretin Weight Loss in Obesity Trials

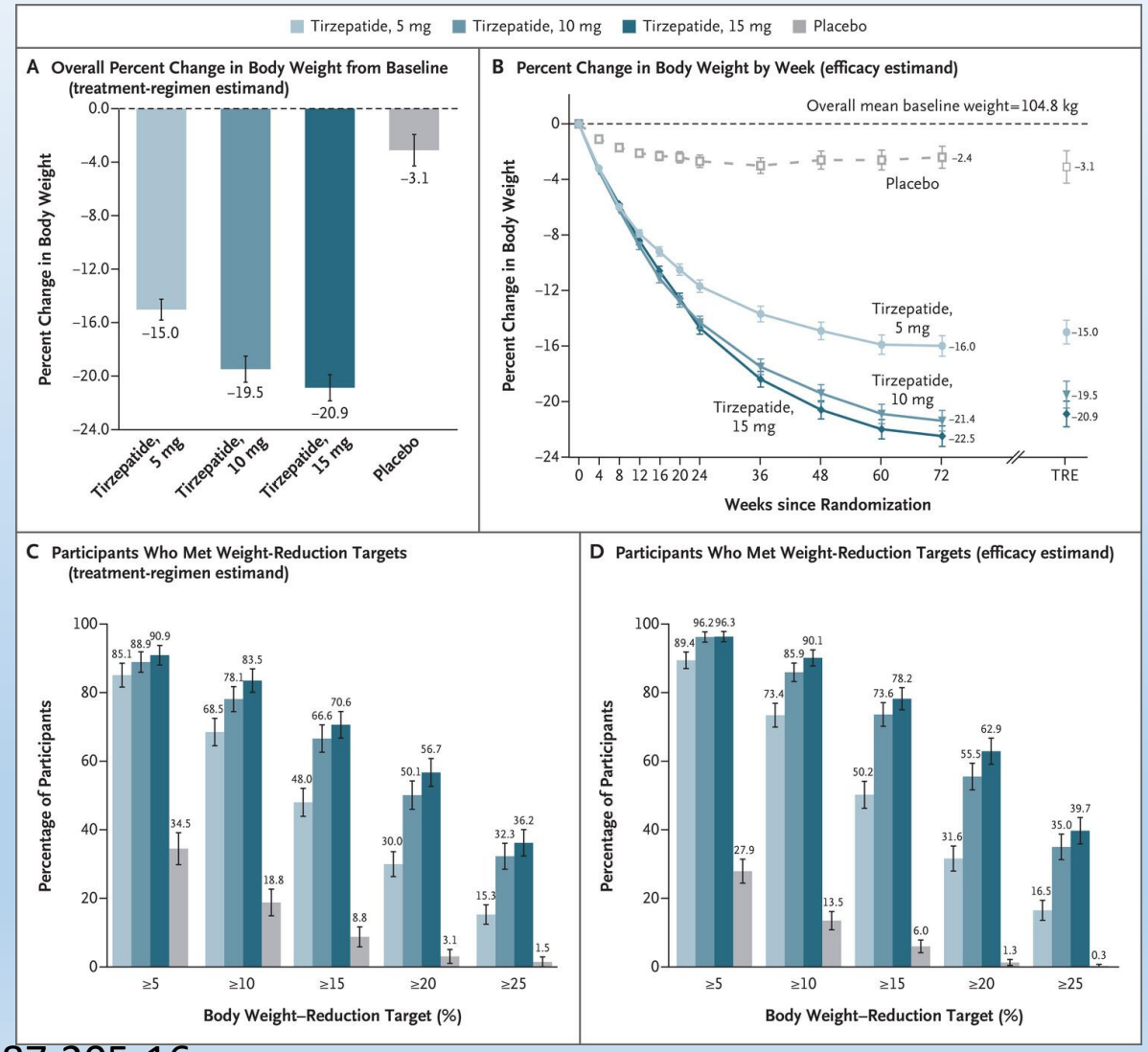
	Liraglutide SCALE	Semaglutide STEP 1	Tirzepatide SURMOUNT
Wt. loss (kg)	-5.6 kg	-12.7 kg	-21.2 kg
% Wt loss	-5.4%	-12.4%	-17.8%
>5% Wt loss	63.2% vs 27.1%	86.4% vs 31.5%	90.9% vs 34.5%
>10% Wt loss	33.1% vs 10.6%	69.1% vs 12.0%	83.5% vs 18.8%
>15% Wt loss		50.5% vs 4.9%	70.6% vs 8.8%
>20% Wt loss		32.0% vs 1.7%	56.7% vs 3.1%

(SCALE) Pi-Sunyer, et al. NEJM 2015:373;11-22, (STEP) Wilding, et al. NEJM 2021:384;989-1002, (SURMOUNT) Jastreboff, et al. NEJM 2022:387;205-16

Why Better Results in Obesity Trials?

- Not diabetes patients
  - Not trying to lose weight in diabetes trials
  - There may be some degree of resistance to hormonal effects in patients with diabetes
- Higher doses
  - While A1c effects have a fairly flat dose-response curve, weight loss does respond better with higher doses
    - Probably secondary to better effects in the brain on satiety with higher doses
- Longer duration
  - Weight loss plateau is much later than A1c plateau

Tirzepatide Dose-Response



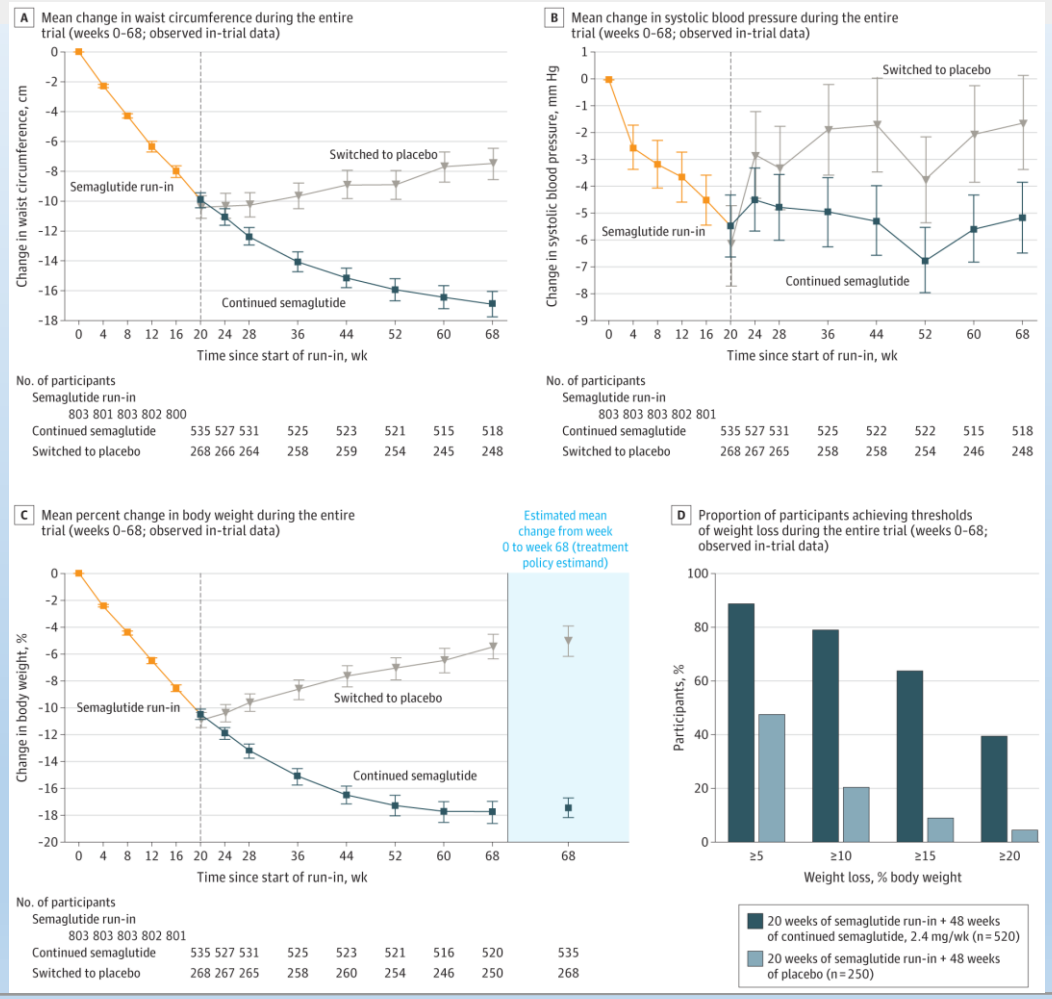
Jastreboff, et al. NEJM 2022:387;205-16

Downsides of Incretin Treatment

- COST!!!
- AVAILABILITY!
- Durability
- Nausea/Vomiting
  - Class effect that is also dose-dependent in the short term
    - Not strictly due to delayed gastric emptying
  - Tachyphylaxis does often occur when slowly titrated
- Other GI
  - Gastroparesis, though tachyphylaxis also occurs with slow titration
  - Diarrhea/constipation

From: **Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial**

JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224



Why Is Tirzepatide Better?

- GIP additive/synergistic?
- GIP effect enables tolerating higher GLP-1 RA doses?
  - May reduce the nausea?
- Perhaps a “super-GLP-1 RA”?

GIP Effects in Obesity

- By promoting fat deposition, GIP may promote obesity
  - In mouse models, receptor knock-outs or antagonists prevent weight gain in obese models, and promote modest weight loss
  - Infusions of GIP are associated with increased release of proinflammatory cytokines from adipocytes
- Stimulation of GIP receptors in the hypothalamus may reduce food intake and body weight
  - Intracerebroventricular or peripheral infusion of GIP achieves this in mouse models, and potentiates GLP-1 induced weight loss
  - Inhibitory signaling may also reduce chemoreceptor nausea

Liu, Frontiers Endcrinol 2024:15;1431292

Bottom Line

- GLP-1 RA or co-agonists are clearly the most effective weight loss drugs we have ever had

- Their efficacy begins to rival bariatric surgery, but requires long term use for maintenance of weight loss

Cardiovascular Risk Reduction

Question 6

- True or False. All GLP-1 RAs have demonstrated reductions in Major Adverse Cardiovascular Events (MACE) in high-risk patients with type 2 diabetes.
  - True
  - False

Question 7

- Which of the following drugs has demonstrated reductions in MACE in high-risk patients WITHOUT Type 2 diabetes?
  - Tirzepatide
  - Liraglutide
  - Semaglutide SC
  - Sitagliptin

Incretins in Cardiovascular Disease

- GLP-1 RA use is associated with blood pressure reduction in hypertensive patients
  - Weight loss may be additive, but effects occur even in absence
    - Effects on receptors in kidney to reduce fibrosis and increase sodium excretion?
- Some evidence of reduced platelet aggregation in patients with obesity treated with liraglutide
- Both GIP and GLP-1 appear to reduce inflammation in vascular tissue

Drucker & Holst, Diabetalogia 2023: 66; 1765-79

The Rosiglitazone Debacle

- For decades, the FDA approved diabetes medications solely based on their ability to lower blood glucose
- In 2007, a meta-analysis of rosiglitazone suggested that its use increased the risk of myocardial infarction (MI) and cardiovascular (CV) death
- Much debate ensued…
- Eventually, the FDA mandated that drugs for diabetes had to demonstrate CV safety, even in high-risk populations, before approval

Nissen & Wolski, NEJM 2007;356:2457-2471

DPP4 Inhibitors

	Saxagliptin SAVOR-TIMI (2013)	Alogliptin EXAMINE (2013)	Sitagliptin TECOS (2015)	Linagliptin CARMELINA (2019)
N, duration	16492 pts 2.1 yrs	5380 pts 1.5 yrs	14671 pts 3.0 yrs	6979 pts 2.2 yrs
Inclusion	DM + CVD or risk	DM, recent ACS	DM + CVD	DM + CVD/renal risk
Primary Endpoint	3 pt MACE HR 1.00 (0.89-1.12)	3 pt MACE HR 0.96 (p=0.32)	4 pt MACE HR 0.98 (0.89-1.08)	3 pt MACE HR 1.02 (0.89-1.17)

(SAVOR) Scirica, et al. NEJM 2013;369:1317-26, (EXAMINE) White, et al. NEJM 2013;369:1327-35,
(TECOS) Green, et al. NEJM 2015;373:232-42, (CARMELINA) Rosenstock, et al. JAMA. 2019;321(1):69-79

DPP4 Inhibitors

	Saxagliptin SAVOR-TIMI (2013)	Alogliptin EXAMINE (2013)	Sitagliptin TECOS (2015)	Linagliptin CARMELINA (2018)
CV Death	HR 1.03 (0.87-1.22)	HR 0.85 (0.66-1.10)	HR 1.03 (0.89-1.19)	HR 0.96 (0.81-1.14)
MI	HR 0.95 (0.80-1.12)	HR 1.08 (0.88-1.33)	HR 0.95 (0.81-1.11)	HR 1.12 (0.90-1.40)
Stroke	HR 1.11 (0.88-1.39)	HR 0.91 (0.55-1.50)	HR 0.97 (0.79-1.19)	HR 0.91 (0.67-1.23)
HF Hosp	HR 1.27 (1.07-1.51)	HR 1.19 (0.90-1.58)	HR 1.00 (0.83-1.20)	HR 0.90 (0.74-1.08)

(SAVOR) Scirica, et al. NEJM 2013;369:1317-26, (EXAMINE) White, et al. NEJM 2013;369:1327-35, (TECOS) Green, et al. NEJM 2015;373:232-42, (CARMELINA) Rosenstock, et al. JAMA. 2019;321(1):69-79

DPP4 Inhibitor Bottom Line

- No cardiovascular benefit from any of them
- No cardiovascular risk either, based on primary endpoint
- Heart failure risk is an open question
  - Are saxagliptin/alogliptin actually worse, or just one of those things with secondary endpoints?
    - Labels all have HF as warning, but not contraindication
  - Absolute increases in risk are smaller than risk seen with TZDs

GLP-1 RA

- -atides (exendin-4 derivatives)
  - Exenatide
  - Lixisenatide*
- -glutides (GLP-1 derivatives)
  - Liraglutide
  - Dulaglutide
  - Semaglutide
  - Albiglutide*

-atides

	Lixisenatide ELIXA (2015)	Exenatide ER EXSCEL (2017)
N, duration	6068 pts 2.1 yrs	14752 pts 3.2 yrs
Inclusion	DM + recent ACS	DM ± CVD
Primary Endpoint	4 pt MACE HR 1.02 (0.89-1.17)	3 pt MACE HR 0.91 (0.83-1.00)

(ELIXA) Pfeffer, et al. NEJM 2015;373: 2247-57, (EXSCEL) Holman, et al. NEJM 2017;377:1228-1239

-atides

	Lixisenatide ELIXA (2015)	Exenatide ER EXSCEL (2017)
CV Death	HR 0.98 (0.78-1.22)	HR 0.88 (0.76-1.02)
MI	HR 1.03 (0.87-1.22)	HR 0.97 (0.85-1.10)
Stroke	HR 1.12 (0.79-1.58)	HR 0.85 (0.70-1.03)
HF Hosp	HR 0.96 (0.75-1.23)	HR 0.94 (0.78-1.13)

(ELIXA) Pfeffer, et al. NEJM 2015;373: 2247-57, (EXSCEL) Holman, et al. NEJM 2017;377:1228-39

-Glutides

	Liraglutide LEADER (2016)	Semaglutide SUSTAIN-6 (2016)	Albiglutide HARMONY (2018)	Dulaglutide REWIND (2019)
N, duration	9340 pts 3.8 yrs	3297 pts 2.1 yrs	9463 pts 1.6 yrs	9901 pts 5.4 yrs
Inclusion	DM + cardio/renal dz or risk	DM + cardio/renal dz or risk	DM + CVD	DM + CVD or risk
Primary Endpoint	3 pt MACE HR 0.87 (0.78-0.97)	3 pt MACE HR 0.74 (0.58-0.95)	3 pt MACE HR 0.78 (0.68-0.90)	3 pt MACE HR 0.88 (0.79-0.99)

(LEADER) Marso, et al. NEJM 2016;375:311-22, (SUSTAIN-6) Marso et al. NEJM 2016;375:1834-44,
(HARMONY) Hernandez, et al. Lancet 2018;392:1519-29, (REWIND) Gerstein, et al. Lancet 2019;394:121-30

-Glutides

	Liraglutide LEADER (2016)	Semaglutide SUSTAIN-6 (2016)	Albiglutide HARMONY (2018)	Dulaglutide REWIND (2019)
CV Death	HR 0.78 (0.66-0.93)	HR 0.98 (0.65-1.48)	HR 0.93 (0.73-1.19)	HR 0.91 (0.78-1.06)
MI	HR 0.86 (0.73-1.00)	HR 0.74 (0.51-1.08)	HR 0.75 (0.61-0.90)	HR 0.96 (0.79-1.15)
Stroke	HR 0.86 (0.71-1.06)	HR 0.61 (0.38-0.99)	HR 0.86 (0.66-1.14)	HR 0.76 (0.61-0.95)
HF Hosp	HR 0.87 (0.73-1.05)	HR 1.11 (0.77-1.61)	---	HR 0.93 (0.77-1.12)

(LEADER) Marso, et al. NEJM 2016;375:311-22, (SUSTAIN-6) Marso et al. NEJM 2016;375:1834-44, (HARMONY) Hernandez, et al. Lancet 2018;392:1519-29, (REWIND) Gerstein, et al. Lancet 2019;394:121-30

Semaglutide PO

	Oral Semaglutide PIONEER (2019)
N, duration	3183 15.9 mo
Inclusion	DM + cardio/renal dz or risk
Primary Endpoint	3 pt MACE HR 0.79 (0.57-1.11)

	Oral Semaglutide PIONEER (2019)
CV Death	HR 0.49 (0.27-0.92)
MI	HR 1.18 (0.73-1.90)
Stroke	HR 0.74 (0.35-1.57)
HF Hosp	HR 0.86 (0.48-1.55)

Husain, et al. NEJM 2019;381:841-51

Semaglutide in Obesity

	Semaglutide SC SELECT (2023)
N, duration	17604 34.2 mo
Inclusion	BMI 27+ and ASCVD
Primary Endpoint	3 pt MACE HR 0.80 (0.72-0.90)

	Semaglutide SC SELECT (2023)
CV Death	HR 0.85 (0.71-1.01)
MI	HR 0.72 (0.61-0.85)
Stroke	HR 0.93 (0.74-1.15)
HF Hosp	HR 0.79 (0.60-1.03)

Lincoff, et al. NEJM 2023;389:2221-2232

GLP-1 RA Bottom Line

- -glutides consistently reduce 3 pt MACE, typically with some reduction in each endpoint. All current injectible ones have FDA approval for CV risk reduction in patients with diabetes.
  - Semaglutide po, not quite
  - -atides do not have indication, though exenatide got close
- Semaglutide sc is the only one approved for CV risk reduction outside of patients with diabetes
- No clear benefit or risk for HF
- Note that albiglutide and dulaglutide achieved reductions in MACE without significant weight loss

Tirzepatide?

- SURPASS-CVOT is underway
  - Comparing itself with dulaglutide in non-inferiority trial
  - Has enrolled 13,299 patients with diabetes and high CV risk
  - Maybe completed in 2025?
  - Also SURMOUNT-MMO (in obesity)

- No signal of increased events in either diabetes or obesity trials

Nicholls, et al. Am Heart J 2024:267;1-11

Possible New Indications

Question 8

- Which of the following drugs has demonstrated reductions in hard renal composite endpoints, specifically in patients with diabetic kidney disease?
  - Tirzepatide
  - Semaglutide SC
  - Dulaglutide
  - Liraglutide

Question 9

- In clinical trials to date, which of the following drugs has shown the greatest potential benefit for sleep apnea?
  - Liraglutide
  - Semaglutide SC
  - Exenatide ER
  - Tirzepatide

Heart Failure with Preserved Ejection Fraction

- For a long time, obesity was seen mostly as a comorbidity for heart failure, especially with preserved ejection fraction (HFpEF). Evidence for a causative role is accumulating.
  - Mechanical effects on heart
    - Hypertrophy, epicardial fat limiting filling
  - Neurohormonal effects on heart
    - Proinflammatory cytokines from visceral fat promote activation of sympathetic and RAAS systems which can result in remodeling
  - Deposition of fat in organs impairs function
    - Fluid retention in kidneys, impaired muscle function

Borloug, et al. Cardiovascular Research 2022;118:3434-50

Heart Failure with Preserved Ejection Fraction

	Semaglutide sc STEP-HFpEF (2023)	Semaglutide sc STEP-HFpEF DM (2024)
N, duration	529 52 weeks	616 52 weeks
Inclusion	BMI 30+ & HFpEF	BMI 30+ & HFpEF & DM
Primary Endpoint	Change in Symptoms & Body weight	Change in Symptoms & Body weight

	Semaglutide sc STEP-HFpEF (2023)	Semaglutide sc STEP-HFpEF DM (2024)
Symptom score	7.8 (4.8-10.9)	7.3 (4.1-10.4)
Body weight	-10.7% (-11.9 to -9.4%)	-6.4% (-7.5 to -5.2%)

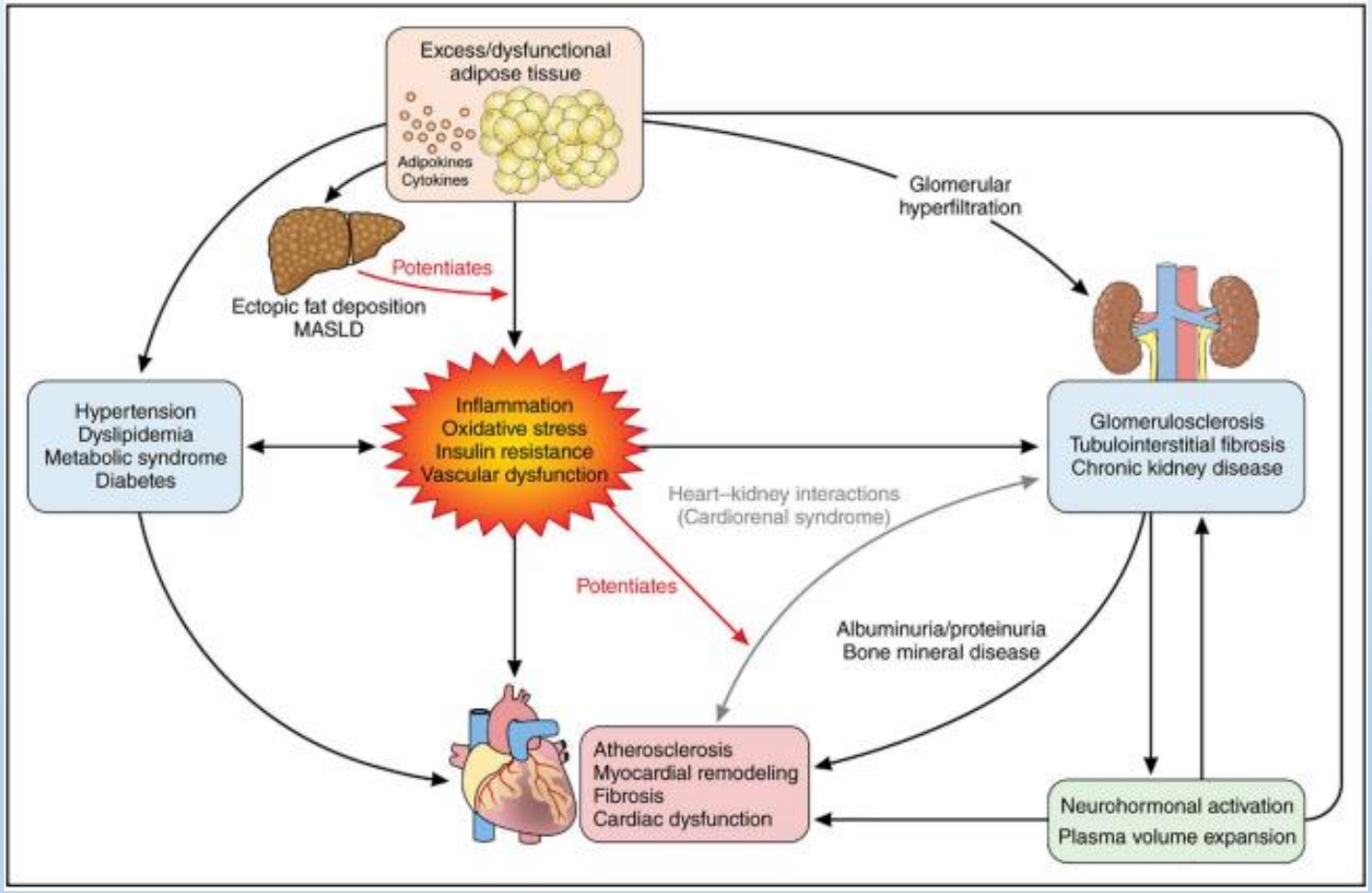
Kosiborod, et al. NEJM 2023;389:1069-84, Kosiborod, et al. NEJM 2024;390:1394-1407

Chronic Kidney Disease (CKD)

- Cardiovascular disease and chronic kidney disease share many common risk factors, and the presence of one increases the risk of developing the other
  - Obesity is one of those common risk factors, diabetes another
  - Cardiovascular-Kidney-Metabolic (CKM) Syndrome is now being promulgated by the American Heart Association
- Unclear if there are direct effects of incretins on the kidney
  - Potential for reduction in inflammation and fibrosis

Ndumele, et al. Circulation 2023;148:1636-64

CKM Conceptual Diagram



Ndumele, et al. Circulation 2023;148:1636-64

CKD Endpoints in GLP-1 RA CV Trials

- LEADER (liraglutide)
  - Endpoint – composite of new macroalbuminuria, doubling serum creatinine, end-stage renal disease, renal death
    - 15.0% vs 19.0% (HR 0.78; CI 0.67-0.92)
- SUSTAIN-6 (semaglutide)
  - Endpoint - composite of new macroalbuminuria, doubling serum creatinine with CrCl<45, and dialysis
    - 3.8% vs 6.1% (HR 0.64; CI 0.46-0.88)
- REWIND (dulaglutide)
  - Endpoint - composite of new macroalbuminuria, eGFR decline of 30+%, and dialysis
    - 17.1% vs 19.6% (HR 0.85; CI 0.77-0.93)

Mann, et al. NEJM 2017;377:839-48, Marso et al. NEJM 2016;375:1834-44, Gerstein, et al. Lancet 2019;394:121-30

Semaglutide in Patients with CKD

	Semaglutide sc FLOW (2024)
N, duration	3533 pts 3.4 yrs
Inclusion	DM + CKD (eGFR 25-75, with varying albuminuria)
Primary Endpoint	composite of the onset of kidney failure, at least a 50% reduction in the eGFR, or death from kidney-related or cardiovascular causes

	Semaglutide sc FLOW (2024)
Primary	HR 0.76 (0.66-0.88)
Annual change eGFR	-2.19* vs -3.36
Change UACR (vs baseline at 2 yr)	0.60* vs 0.88
MACE	12.0% vs 14.4% (HR 0.82*)

Perkovic, et al. NEJM 2024;391:109-21

Obstructive Sleep Apnea (OSA)

- Obesity is a major risk factor for OSA
- Diabetes, even without obesity, is also a major risk factor
- Positive Airway Pressure (PAP) improves apnea-hypopnea index (API) and subsequent daytime sleepiness, but is highly dependent on adherence
- Various surgical interventions, including bariatric surgery, and a few devices can help, but no medications are approved

Incretins in Patients with OSA

	Liraglutide sc SCALE (2016)
N, duration	359 pts 32 weeks
Inclusion	Obesity + mod-severe hypopnea (15+ events/hr)
Primary Endpoint	Change in AHI

	Liraglutide sc SCALE (2016)
AHI Change	-6.1/hr [12.4%] (-11.1 to -1.2)
Body weight	-4.9 kg [-4.2%] (-6.2 to -3.7)

Blackman, et al. Int J Obes 2016;40:1310-19

Incretins in Patients with OSA

	Tirzepatide sc SURMOUNT-OSA (2024)
N, duration	234/235 pts 52 weeks
Inclusion	Obesity + mod-severe hypopnea ± PAP
Primary Endpoint	Change in AHI

	SURMOUNT -OSA 1 (2024)	SURMOUNT -OSA 2 (2024)
AHI Change	-20.0 [47.7%] (-25.8 to -14.2)	-23.8 [56.2%] (-29.6 to -17.9)
Body weight	-16.1 % (-18.0 to -14.2)	-17.3% (-19.3 to -15.3)

Malhotra, et al. NEJM 2024; DOI: 10.1056/NEJMoa2404881

Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD)

- Often defined as evidence of liver damage (increased ALT) in combination with at least one element of metabolic syndrome
  - Increased fat deposition in liver, accompanied by inflammation and fibrosis
  - By 2040, half of adults world-wide may have MASLD
  - Can progress to Metabolic-Associated Steatohepatitis (MASH), then to cirrhosis, and then to hepatocellular carcinoma
- While no GLP-1 or GIP receptors in the liver, benefits may be seen with weight loss or reduction in inflammation

Yanai, et al. Int J Mol Sci 2023;24:15473

Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD)

- LEAN (liraglutide, diabetes doses)
  - Endpoint – histological improvement without worsening fibrosis
    - 39% vs 9%, p=0.019
    - No significant difference in transaminases or inflammation
- Newsome, et al. (daily semaglutide)
  - Endpoint – resolution of MASH without worsening fibrosis
    - 0.1 mg – 40%
    - 0.2 mg – 36%
    - 0.4 mg – 59% ($p<0.001$)
    - Placebo – 17%
      - 0.4 mg dose did see significant reductions in transaminases vs placebo

Armstrong, et al. Lancet 2016;387:679-90, Newsome, et al. NEJM 2021;384:1113-24

Parkinson's Disease (PD)

- Parkinson's is a progressive neurologic disorder marked by destruction of dopaminergic neurons in the CNS.
  - Results in motor symptoms, as well as autonomic and cognitive symptoms over time
  - Diabetes is a risk factor for developing PD. Insulin resistance is associated with increased α-synuclein aggregates
- Observationally, use of DPP4 inhibitors and GLP-1 RA is associated with significantly reduced risk of PD
- GLP-1 receptors are found in the brain. Could potentially reduce neuroinflammation directly or through increased insulin

Brauer, et al. Brain 2020;10: 3067-76, Standaert, NEJM 2024;390:1233-34

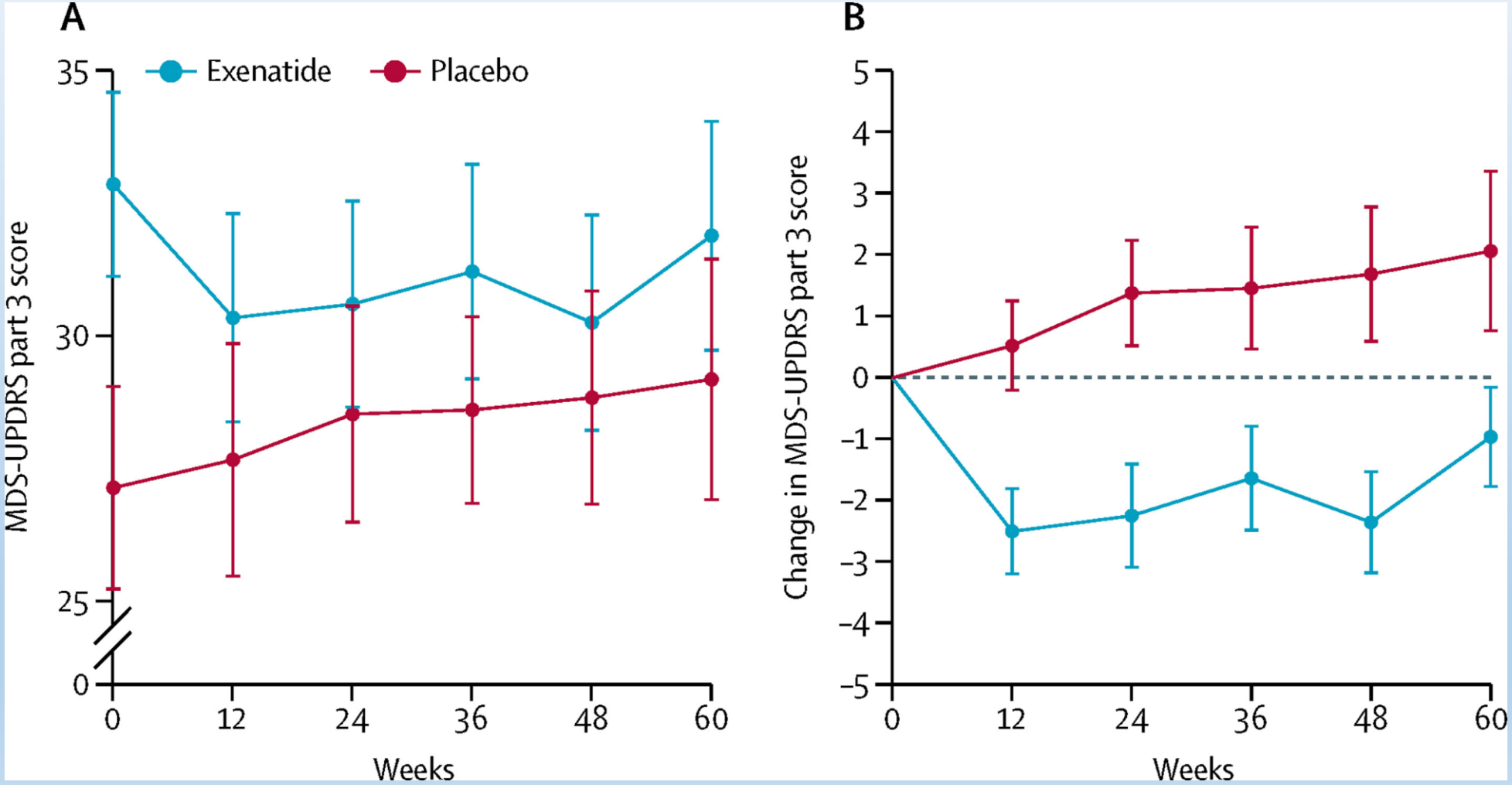
Parkinson's Disease

	Exenatide ER EXENATIDE-PD (2017)	Lixisenatide LIXIPARK (2024)
N, duration	60 60 weeks	156 12 mo
Inclusion	Mild-mod PD on DA tx	Mild-mod PD on DA tx
Primary Endpoint	Change in movement score after 12 week washout	Change in movement score at 1 yr

	Exenatide ER EXENATIDE-PD (2017)	Lixisenatide LIXIPARK (2024)
Movement score (end tx)	-4.3 (-7.1 to -1.6)	-3.08 (-0.86 to -5.30)
Movement score (post-washout)	-3.5 (-6.7 to -0.3)	-3.0 (-0.1 to -5.8)

Athauda, et al. Lancet 2017;390:1664-75, Meissner, et al. NEJM 2024;390:1176-85

Parkinson's Disease



Athauda, et al. Lancet 2017;390:1664-75

Substance Use Disorders

- Satiety is intertwined with reward pathways in the brain
- Various animal models have indicated reductions in substance abuse with the use of GLP-1 RA
  - Alcohol, nicotine, cocaine, opioids…
- Observational studies, case series, and anecdotal data support benefits GLP-1 RA for reductions in smoking and alcohol consumption in humans

Leggio, et al. Nature Med 2023;29:2993-95, Volkow & Xu, Addiction 2024; doi: 10.1111/add.16626

Substance Use Disorders

- Klausen, et al.
  - In 127 patients with alcohol use disorder randomized to exenatide ER or placebo for 26 weeks, there was a reduction in heavy drinking days and total alcohol intake, but no difference between groups
    - Potential benefit in those with BMI 30+
- Yammine, et al.
  - In 84 overweight smokers, exenatide ER increased smoking abstinence over placebo (46.3% vs 26.8%)
- Lengsfeld, et al
  - In 255 smokers, dulaglutide did not improve smoking cessation over placebo (63% vs 65%), but did prevent weight gain

Klausen et al., JCI Insight 2022;7:e159863, Yammine, et al. Nicot Tob Res 2021;23:1682-90,
Lengsfeld, et al. EClinicalMedicine 2023;57; doi: 10.1016/j.eclinm.2023.10186

Additional Combinations in Trials

Question 10

- Which of the following compounds has proven problematic for the treatment of obesity?
  - GIP antagonist
  - Amylin agonist
  - Glucagon antagonist
  - Glucagon agonist

GLP-1 RA + GIP Antagonist

- Why consider a GIP antagonist if an agonist works so well?
  - GIP does promote fat accumulation in adipocytes
  - GIP receptor knockout mice are protected from weight gain
- Maridebart cafraglutide
  - Anti-GIP receptor antibody linked to two GLP-1 analogue peptides
  - Mean half-life approximately 2 weeks
  - Phase 1 in humans showed significant weight loss
    - Single 840 mg dose - -8.2% at day 92 (appears same at day 150)
    - Three doses of 420 mg q4w - -14.5% at day 85 (-11.5% 150d post last dose)
    - Safety appears similar to other GLP-1 RA (mostly nausea)

Veniant, et al. Nat Metab 2024;6:290-303

Amylin Additives

- Amylin is made by β-cells of pancreas, and co-excreted with insulin. Also synthesized in areas of the brain.
  - Pramlintide is an analogue currently approved, for both type 1 & type 2 diabetes
- Effects are qualitatively similar to GLP-1
  - Increase satiety, decrease gastric emptying and glucagon release
  - Also appears to have both central and peripheral effects
    - May potentially increase leptin sensitivity?
- Pramlintide offers very modest weight loss and A1c benefits
  - Relatively short half-life (~ 45 min)

Dehestani, et al. J Obes Metab Syndr 2021;30:320-5, Holst, Nature Metab 2024; doi: 10.1038/s42255-024-01113-9

Amycretin

- Novel unimolecular amylin and GLP-1 receptor agonist
  - Oral dosage form
- Phase 1 data
  - Enrolled overweight patients without diabetes
  - Different arms with single and multiple ascending doses
  - Weight loss at 12 weeks
    - Amycretin 50 mg daily – 10.4%
    - Amycretin 2x50 mg daily – 13.1%
    - Placebo – 1.2%
  - Safety – frequent, dose-dependent nausea

https://www.medscape.com/viewarticle/remarkable-weight-loss-seen-novel-oral-combination-safe-and-2024a1000glt

Cagrilintide

- Long-acting amylin analog
- Phase 2 Dose-ranging study complete in obesity
  - 0.3 mg to 4.5 mg sc weekly, compared body weight reduction to liraglutide 3.0 mg daily and placebo, administered over 26 weeks
  - Cagrilintide - -6.0% to -10.8%
  - Liraglutide - -9.0%
  - Placebo - -3.0%
  - For 4.5 mg dose:
    - 5+% weight loss – 89%
    - 10+% weight loss – 54%

Lau, et al. Lancet 2021;398:2160-72

Cagrilintide + Semaglutide (CagriSema)

- Phase 2 study complete for type 2 DM (32 weeks)
  - 2.4 mg cagrilintide, 2.4 mg semaglutide, or combo given weekly
  - Pts with BMI 27+ and A1c 7.5-10% on metformin ± SGLT2i

	Avg A1c reduction	% A1c <7	Avg % weight loss	10% weight loss
Cagrilintide (n=30)	-0.9%	33%	-8.1%	23%
Semaglutide (n=31)	-1.8%	69%	-5.1%	14%
CagriSema (n=31)	-2.2%	89%	-15.6%	71%

Frias, et al. Lancet 2021;402:720-30

Glucagon Additives

- Glucagon stimulates glucose release from the liver by enhancing glycogenolysis and increasing gluconeogenesis…
- It also promotes amino acid metabolism and lipid metabolism in the liver
  - Appears to markedly reduce appetite and increase energy expenditure, and may increase insulin sensitivity…
- Glucagon antagonists resulted in:
  - Decreased A1c, but also hyperglucagon secretion resulting from hyperplasia of alpha cells
  - Marked increases in circulating amino acids and LDL, as well as steatosis of the liver, yielding elevated transaminases

Holst, Nature Metab 2024; doi: 10.1038/s42255-024-01113-9, Novikoff & Muller, Peptides 2023;165:171003

Mazdutide (GLP-1/Glucagon coagonist)

- Diabetes (phase II)
  - Doses ranged from 3-6 mg weekly, given over 20 weeks
  - A1c reduced by -1.41% to -1.67%
    - Dulaglutide 1.5 mg - -1.35%, placebo - +0.03%
  - Body weight reduced -4.1% to -7.1%
    - Dulaglutide – 2.7% and placebo -1.4%
- Obesity (phase II)
  - Doses ranged from 3-6 mg weekly, given over 24 weeks
  - Body weight reduced -6.7% to -11.3%
    - Placebo - +1.0%

Zhang, et al. Diabetes Care 2024;47:160-68, Ji, et al. Nat Commun 2023;14:8289

Survodutide (GLP-1/Glucagon coagonist)

- Diabetes (phase II)
  - Doses ranged from 0.3 to 2.7 mg weekly or 1.2 to 1.8 mg BIW (16 w)
  - A1c reduced by -0.91% to -1.71%
    - Semaglutide 1 mg - -1.46%, placebo - -0.15%
  - Body weight reduced -2.5% to -8.7%
    - Semaglutide -5.3%, placebo -0.8%
- Obesity (phase II)
  - Doses ranged from 0.6 to 4.8 mg weekly (46 weeks)
  - Body weight reduced -6.2% to -14.9%
    - Placebo - -2.8%

Bluher, et al. Diabetalogia 2024;67:470-82, le Roux, et al. Lancet Diabet Endocrinol 2024;12:162-73

Survodutide (GLP-1/Glucagon coagonist)

- MASH & Fibrosis (phase II)
  - Doses ranged from 2.4 to 6 mg weekly (48 weeks)
  - Reduction in MASH with no worse fibrosis in 47% to 62%
    - placebo - 14%
  - Decrease liver fat by 30+% in 57-63%
    - placebo - 14%

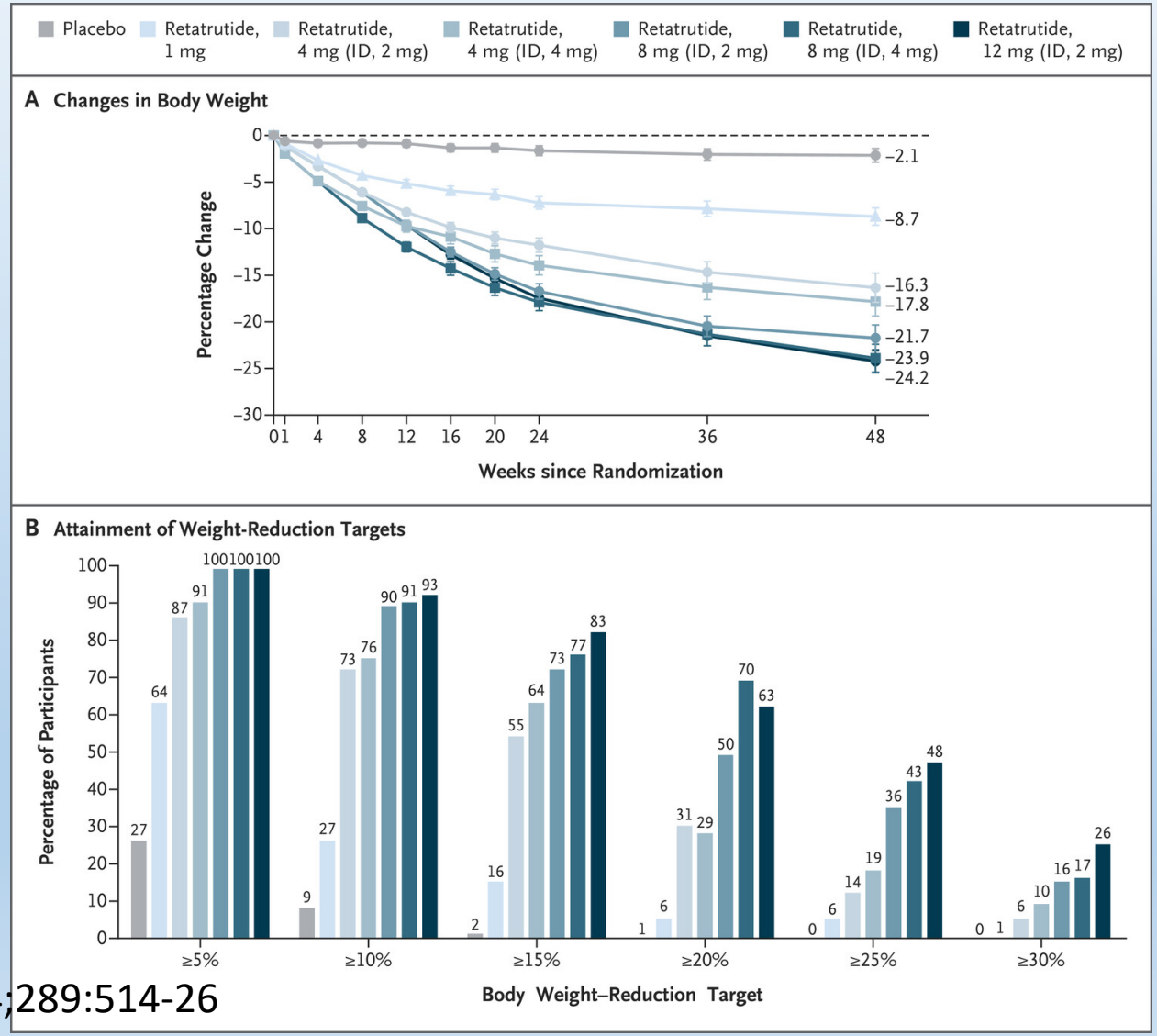
Sanyal, et al. NEJM 2024;391:311-19

Retatrutide (GLP-1/GIP/Glucagon tri-agonist)

- Diabetes (phase II)
  - Doses ranged from 0.5 to 12 mg weekly over 36 weeks
  - A1c at 24 weeks reduced by -0.43 to -2.02%
    - Dulaglutide 1.5 mg - -1.41%, placebo - -0.01%
  - Body weight at 36 weeks reduced -3.19% to -16.94%
    - Dulaglutide – -2.02% and placebo -3.00%
- Obesity (phase II)
  - Doses ranged from 1-12 mg weekly, given over 48 weeks
  - Body weight at 24 weeks reduced -7.2% to -17.5%
    - Placebo - -1.6%
  - Body weight at 48 weeks reduced -8.7% to -24.2%
    - Placebo - -2.1%

Rosenstock, et al. Lancet 2023;402:529-44, Jastreboff, et al. NEJM 2024;289:514-26

Retatrutide (GLP-1/GIP/Glucagon tri-agonist)



Jastreboff, et al. NEJM 2024;289:514-26

Summary

- While incretins were initially defined by their ability to increase insulin secretion in response to food, they have direct and indirect effects on numerous other organs, especially the brain
- GLP-1(±) RAs have varying effects on obesity, with some achieving very significant benefits
- GLP-1 RAs have demonstrated mostly consistent benefits for cardiovascular event reduction in patients with diabetes, even in the absence of weight loss
  - We are starting to see those benefits expanded to patients without diabetes

Summary

- In early clinical trials, GLP-1 RAs have shown strong benefits in those with CKD, OSA, and MASLD
  - Potential benefits in other areas, including certain neurologic conditions
- While tirzepatide, as a dual agonist, is already approved and very effective, combination of GLP-1 agonism with other metabolic hormones is developing a pipeline of potential new drugs for diabetes, obesity, and MASLD.

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Oh, Good Lord…

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Please Make It STOP!!!

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Questions?

CE Evaluation Access Code

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Capital Letters, No spaces, complete by _____

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