Overview: Incretin mimetic drugs and considerations for the anesthesia provider

Presenter: Andy Baum, CRNA

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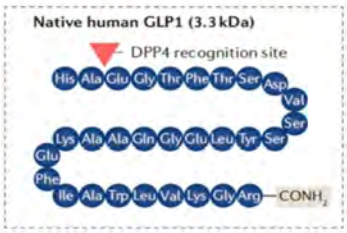
Objectives

- History/ statistics
- Mechanism of Action
- Research to date and beyond- Efficacy, Safety, and outcomes
  - Endocrine
  - Cardioprotective
  - Neuroprotective
- Adverse Effects
- Perioperative anesthesia considerations, recommendations, and management for patients on incretin mimetics medication
- "Round Table"

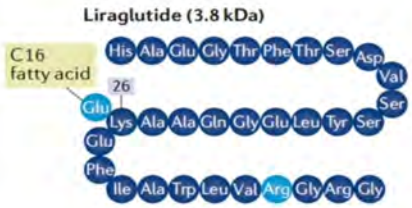
2

History/ statistics

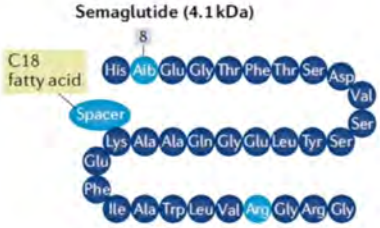
Structure of native GLP-1 compared to approved GLP1 receptor agonists



- Half life = 1-2 minutes



- Half life = 13 hours



- Half life = 165 hours

Andersen, A., Lund, A., Knop, F.K. *et al.* Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol* **14**, 390–403 (2018).
Slide adapted with permission from Dr. Domenica Rubino

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Incretin hormones

Glucagon- Like peptide-1 (GLP-1)

- Hormones released in response to food intake
- Stored in the small and large intestine
- Sends a message to the pancreas (beta cells) to increase insulin release
- Slows the absorption of carbohydrates = decrease postprandial blood glucose
  - DELAYED GASTRIC EMPTYING
- Decreased appetite, less cravings, prolonged satiety
- Metabolized by dipeptidyl peptidase- 4 (DPP-4)
  - Endogenous GLP-1 hormones have a short half life because of these enzymes

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Incretin hormones

Glucose- dependent insulinotropic polypeptide (GIP)

- Produced by cells in the upper small intestine
- Hormones released when glucose interacts with the cells of the upper small intestine
- Sends a message to the pancreas (beta cells) to increase insulin release
  - Alpha cells- increase glucagon *
- Slows the absorption of carbohydrates = decrease postprandial blood glucose
- Decreased appetite

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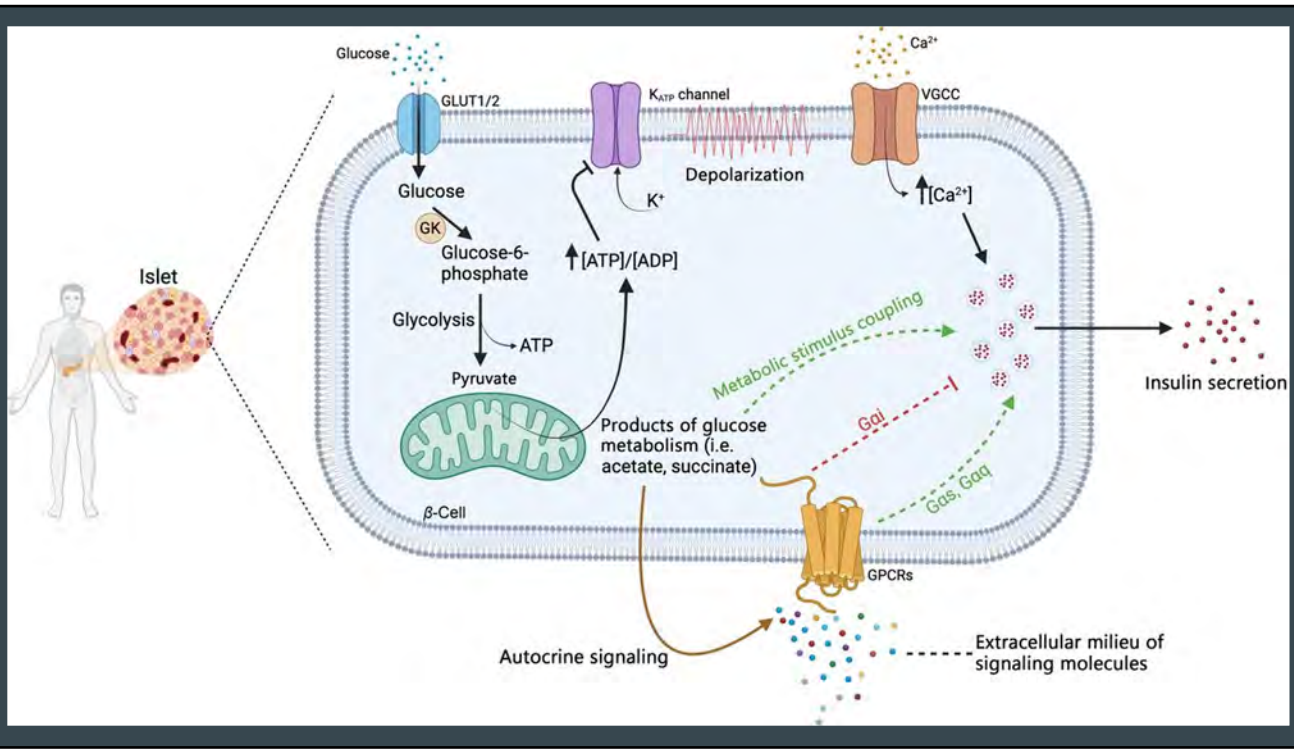

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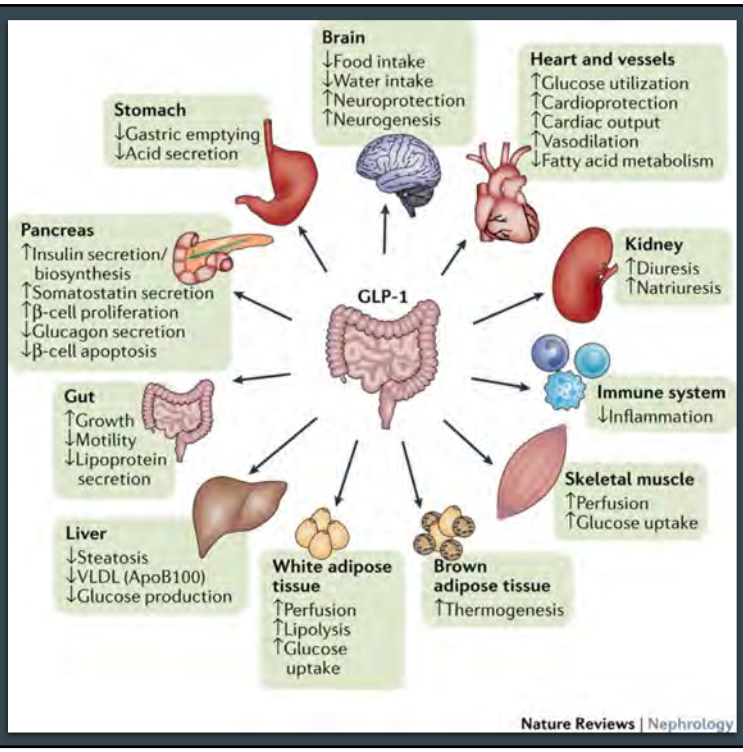

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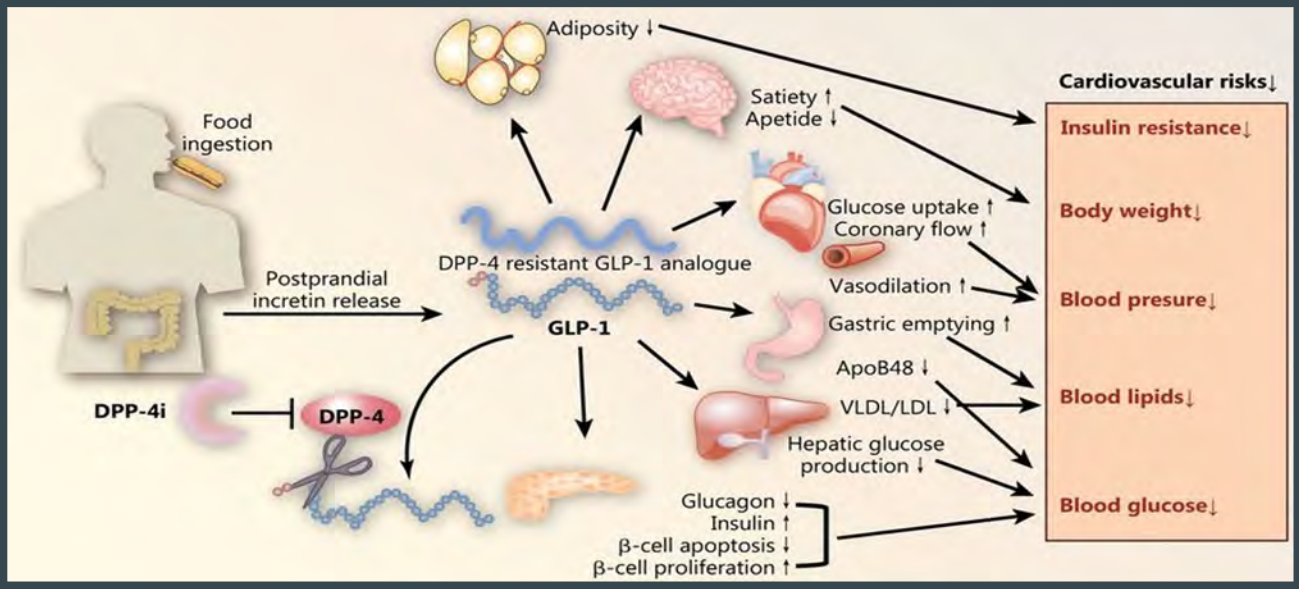
Cardiovascular Risk Reduction



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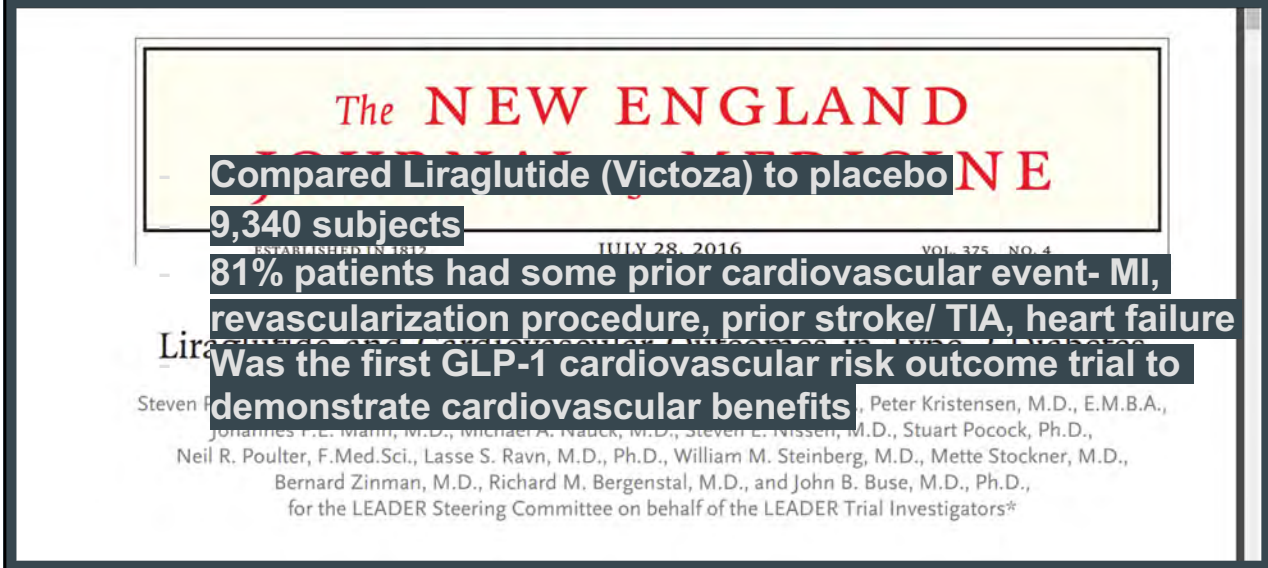
LEADER Trial


The NEW ENGLAND

JULY 28, 2016

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilles Daniels, M.D., Kevin Hess Brown, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

- Compared Liraglutide (Victoza) to placebo
- 9,340 subjects
- 81% patients had some prior cardiovascular event- MI, revascularization procedure, prior stroke/ TIA, heart failure
- Was the first GLP-1 cardiovascular risk outcome trial to demonstrate cardiovascular benefits

Marso, et al NEJM, July 2016

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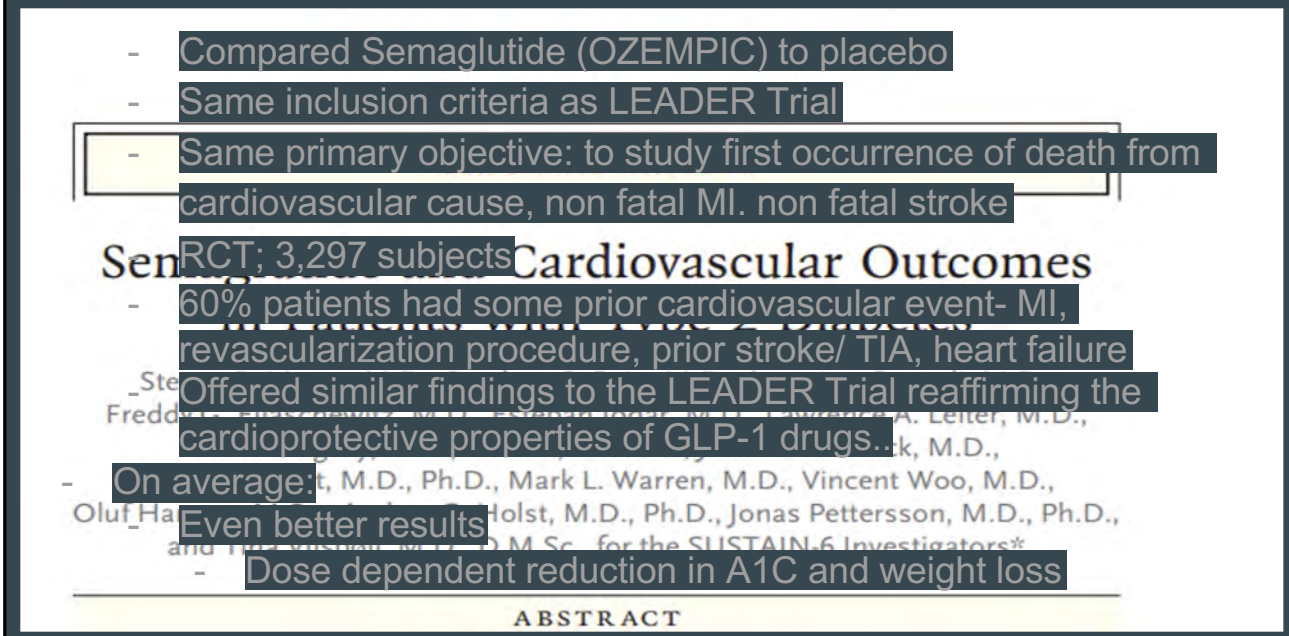
SUSTAIN- 6 Trial


Semaglutide and Cardiovascular Outcomes

Steven P. Marso, M.D., Gilles Daniels, M.D., Kevin Hess Brown, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Thue Vissing, M.D., M.Sc., for the SUSTAIN-6 Investigators*

ABSTRACT

- Compared Semaglutide (OZEMPIC) to placebo
- Same inclusion criteria as LEADER Trial
- Same primary objective: to study first occurrence of death from cardiovascular cause, non fatal MI. non fatal stroke
- RCT; 3,297 subjects
- 60% patients had some prior cardiovascular event- MI, revascularization procedure, prior stroke/ TIA, heart failure
- Offered similar findings to the LEADER Trial reaffirming the cardioprotective properties of GLP-1 drugs..
- On average:
- Even better results
- Dose dependent reduction in A1C and weight loss

S. Marso, et, NEJM, Nov 2016

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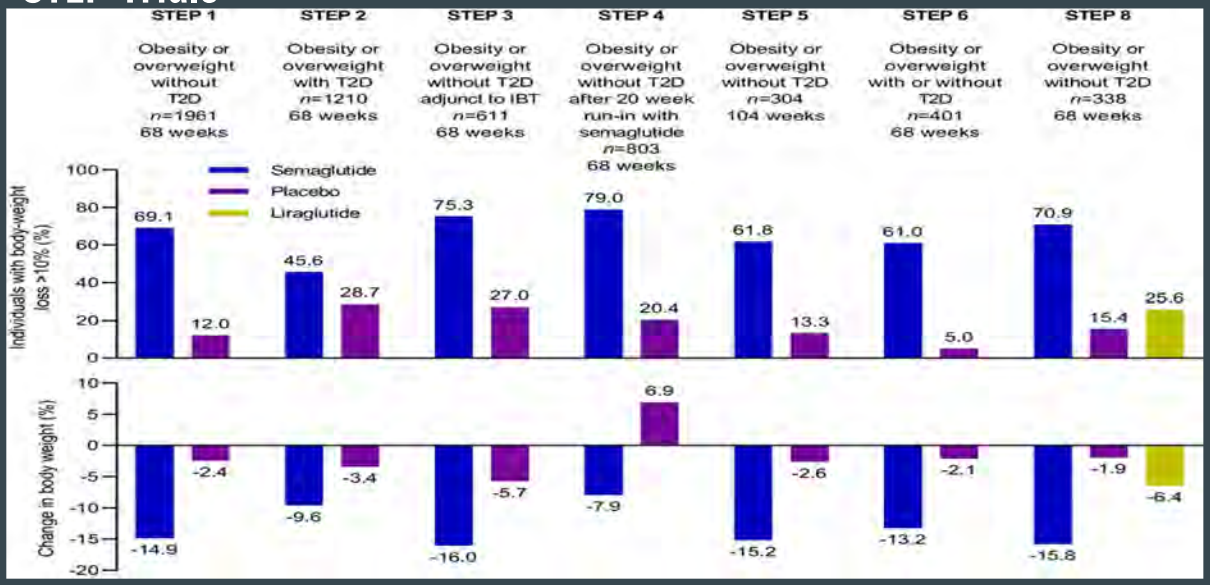
STEP Trials



CR Andreasen et al, Diabetologia, July 2023

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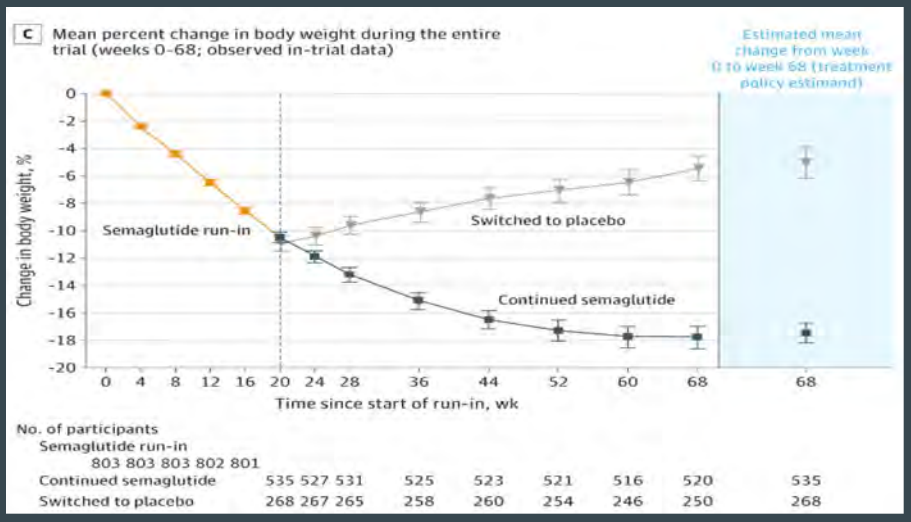
STEP 4- Withdrawal Trial



Rubino, D et al. JAMA 2021.

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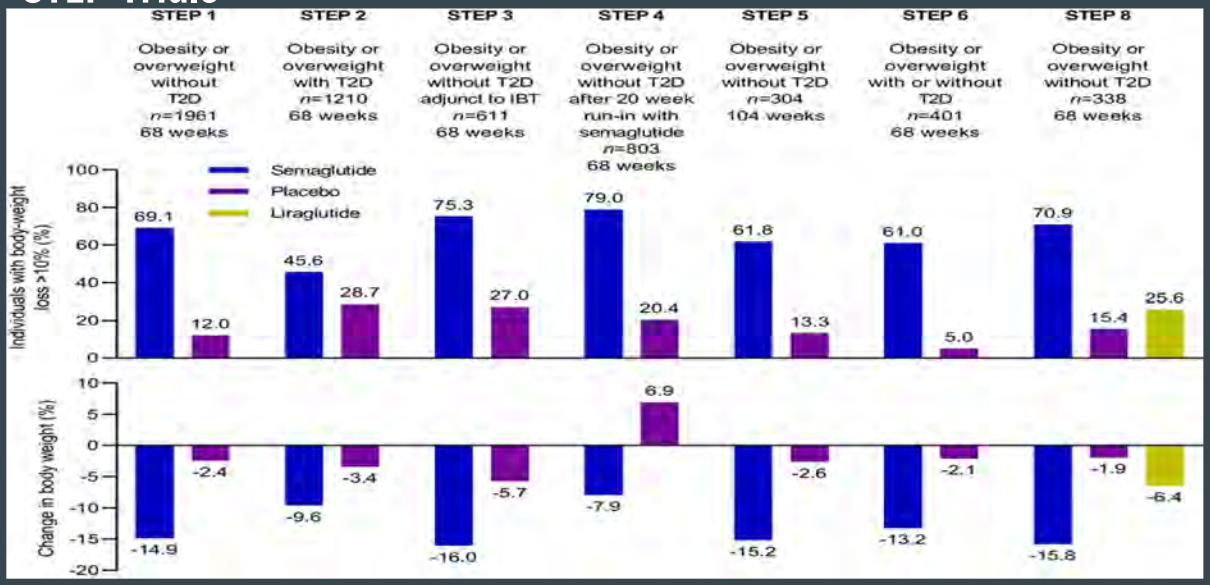
STEP Trials



CR Andreasen et al, Diabetologia, July 2023

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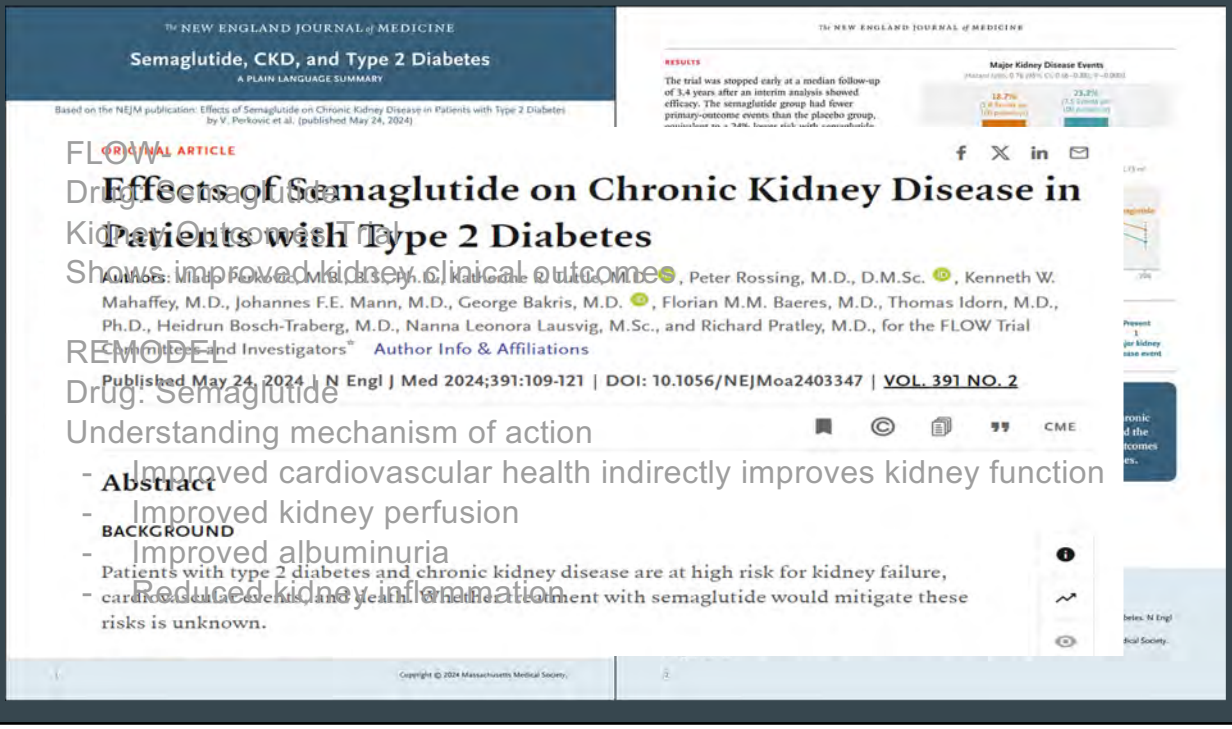

FLOW
Drug: Semaglutide
Kidney Outcomes Trial
Shows improved kidney clinical outcomes

REMODEL
Drug: Semaglutide
Understanding mechanism of action
- Improved cardiovascular health indirectly improves kidney function
- Improved kidney perfusion
- Improved albuminuria
- Reduced kidney inflammation

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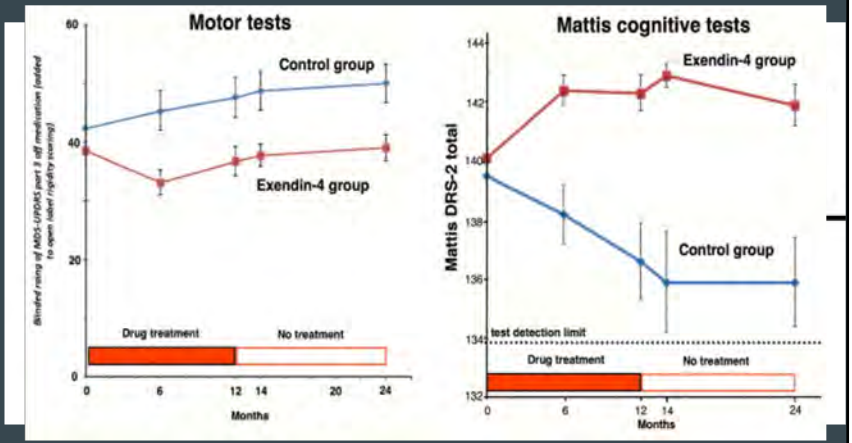
Promising neuroprotective properties

- GLP-1 drugs appear to improve motor and cognitive baseline
- These changes are sustain after stopping the drug which suggest a fundamental change in how the pathology progress
- liraglutide significantly slowed down the deterioration in cognitive impairments
- MRI scans confirm brain changes are slowed



Aviles-Olmos et al., 2013 2014

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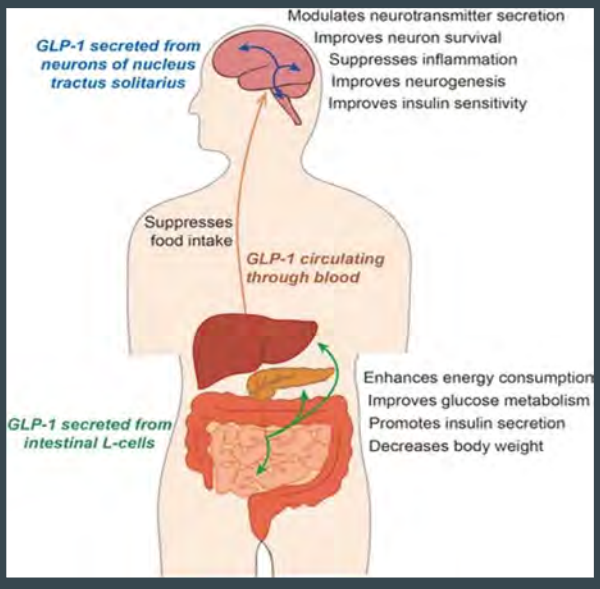
Promising neuroprotective properties

- correlation between CSF drug concentration and therapeutic benefit as a neuroprotective drug
- Poor understanding of exact mechanism of actions
  - anti - inflammatory
  - Normalized energy utilization
  - Cellular repair



Kim, et al Neuropharmacology, Aug 2020

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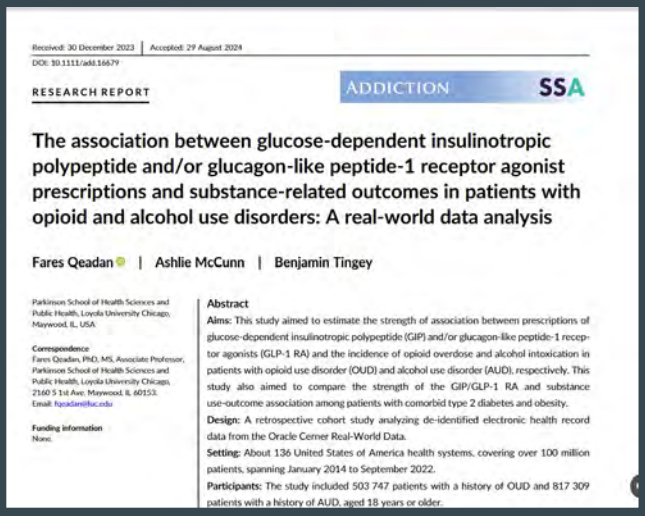
Future

- dual therapy drugs (GLP/GIP)
- triple therapy drugs (GLP/GIP/Glucose)

Speculative:

- Treatment for addiction
  - Alcohol, opioids, gambling, etc..
- Treatment for cancers



Received: 30 December 2023 | Accepted: 29 August 2024
DOI: 10.1111/add.16679

RESEARCH REPORT

ADDICTION SSA

The association between glucose-dependent insulinotropic polypeptide and/or glucagon-like peptide-1 receptor agonist prescriptions and substance-related outcomes in patients with opioid and alcohol use disorders: A real-world data analysis

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Funding information
None.

Abstract

Aims: This study aimed to estimate the strength of association between prescriptions of glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon-like peptide-1 receptor agonists (GLP-1 RA) and the incidence of opioid overdose and alcohol intoxication in patients with opioid use disorder (OUD) and alcohol use disorder (AUD), respectively. This study also aimed to compare the strength of the GIP/GLP-1 RA and substance use-outcome association among patients with comorbid type 2 diabetes and obesity.

Design: A retrospective cohort study analyzing de-identified electronic health record data from the Oracle Cerner Real-World Data.

Setting: About 136 United States of America health systems, covering over 100 million patients, spanning January 2014 to September 2022.

Participants: The study included 503 747 patients with a history of OUD and 817 309 patients with a history of AUD, aged 18 years or older.

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Adverse Outcomes

Top concerns	Muscle loss	GI issues	Vitamin deficiency	Weight Loss Maintenance
Rationale	• More data needed, STEP 1 subgroup analysis demonstrated 40% FFM loss – other data less concerning • Lean mass helps maintain **metabolic rate** and minimizes risk of **osteoporosis, falls, and injuries**	• GLP-1 drugs slow digestion and gastric motility • **Gastrointestinal side effects** include **constipation** and **diarrhea**	• Obesity as well as very low-calorie diets increase risk vitamin and mineral deficiencies, GLP1R agonist therapy may be likened to **vertical sleeve gastrectomy**	• Medication persistence remains and issue – EHR data suggests a large portion of users discontinue GLP-1R agonist therapy • Likely due to a variety of reason
Recommendation	Prioritize **high quality protein**, ideally in 20-30g increments, especially combined with exercise	Soluble **fiber** and insoluble **fiber** & hydration may help with constipation	Be aware of deficiency symptoms – focus on vitamin A, D, E, C, B vitamins, calcium, magnesium, zinc	Data indicates lower carbohydrate approach may limit weight regain

Volek J, et al. Nutritional Considerations During Major Weight Loss. Curr Nutr Rep. 2024., Almanoz JP, et al. Nutritional considerations with AOMs. Obesity. 2024, McKenzie, A.L. and S.J. Athinarayanan, Impact of Glucagon-Like Peptide 1 Agonist Deprescription. Diabetes Ther, 2024.

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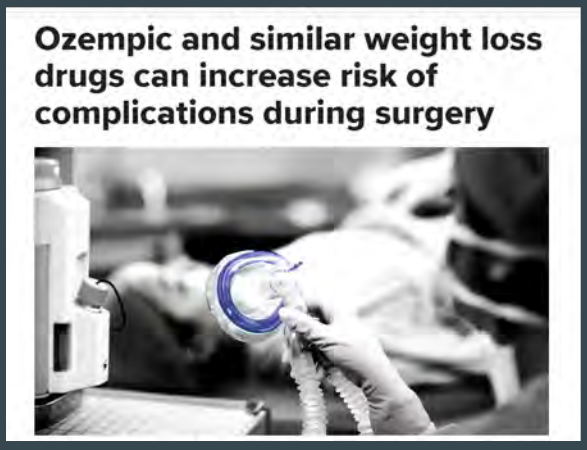
Peri-operative anesthesia considerations, recommendations, and management for patients on GLP-1 medication

Doctors warn some popular weight-loss drugs may raise risk of complications under anesthesia

Health

Patients who take blockbuster drugs like Wegovy or Ozempic for weight loss may face life-threatening complications if they need surgery or other procedures that require empty stomachs for anesthesia. This summer's guidance to halt the medication for up to a week may not go far enough, either.



Ozempic and similar weight loss drugs can increase risk of complications during surgery

ASA Perioperative Guidance for GLP-1 Agonist- June 2023

AANA Perioperative management for patients taking GLP-1 agonist-March 2024

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Consensus/ Clinical Guidelines- Elective Surgery

Days prior to surgery:

- Hold weekly or daily GLP-1 dose prior to surgery
- Consider DM2 management for prolonged GLP-1 pause

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Consensus/ Clinical Guidelines- Elective Surgery

Day of procedure:

-There is no evidence to support safe NPO guidelines for GLP-1 patients

- Evaluate GI symptoms
  - No symptoms / GLP-1 has been held = proceed as normal
  - No symptoms but GLP-1 NOT discontinued= Full stomach precautions; consider POCgUS
  - If symptomatic, consider postpone, cancelation, or proceed as full stomach

- Consider POCgUS

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Consensus/ Clinical Guidelines- Emergent Surgery

Proceed with “Full Stomach” precautions

Consider gastric decompression

Consider awake intubation

22

+

Grand Rounds

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Additional References

"American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-like Peptide-1 (GLP-1) Receptor Agonists." American Society of Anesthesiologists (ASA), www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative. Accessed 8 Sept. 2024.

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