DALLAS OBESITY SOCIETY

GLP1 Receptor Agonist in Obesity Treatment and Beyond

Tonia Vinton, MD – President and Founder of DOS

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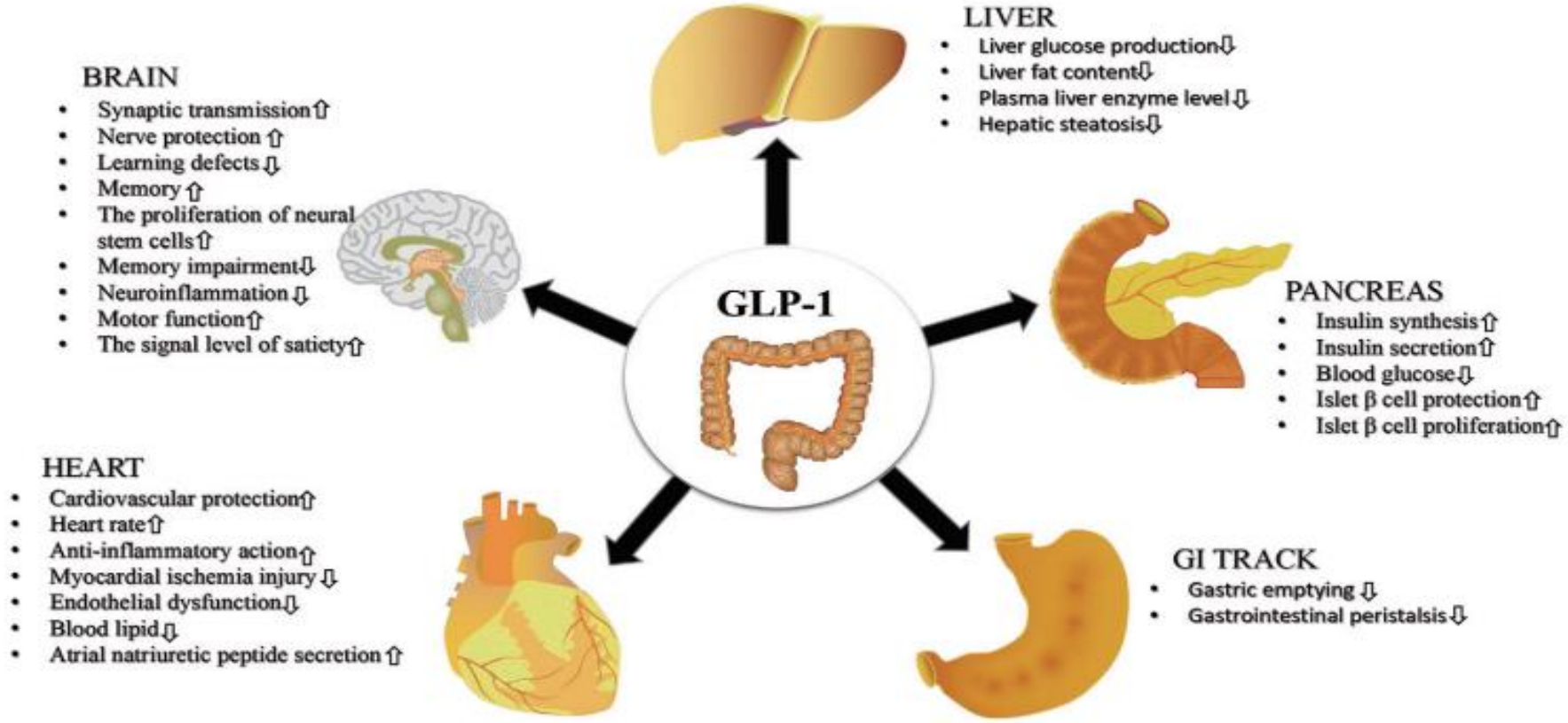
Glucagon like peptide-1 Receptor Agonist



Zhao, Xin et al. "GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects." *Frontiers in endocrinology* vol. 12 721135. 23 Aug. 2021

GLP-1RA and CVD

All CVOT with GLP1-RA show 3-point MACE reduction (CV mortality, non-fatal MI, and non-fatal stroke) and decrease in all cause mortality

Reductions in systolic BP, body weight, and LDL-Cholesterol, as well as increase in heart rate were noted in GLP1-RA

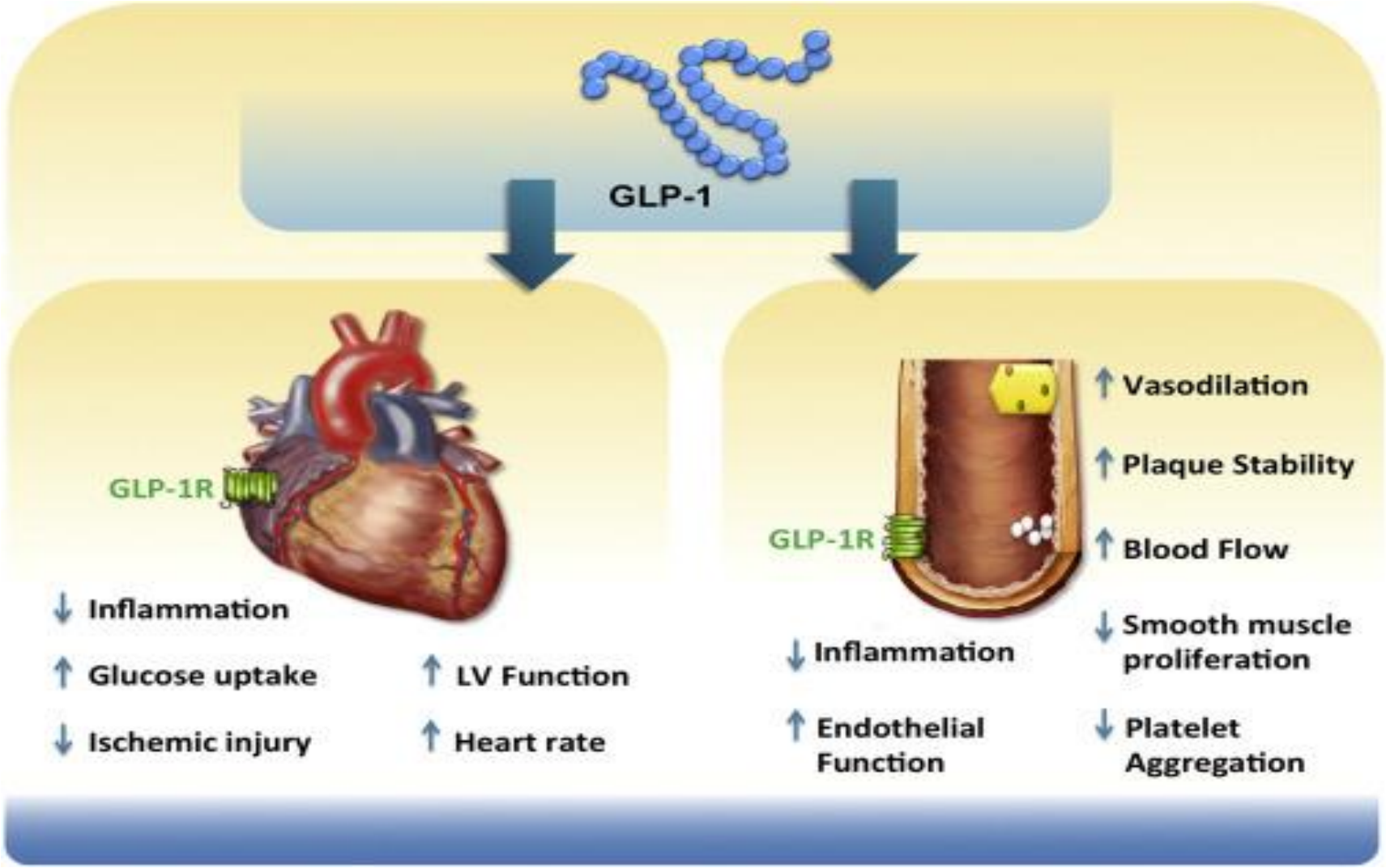
Anti-hypertensive effects are evident after 2 weeks of GLP1-RA treatment (before significant weight loss)

CV benefit is a class effect of GLP-1RA

Prelim evidence for dual agonists (GIP-GLP-1)

Caruso, Irene et al. “Heterogeneity and Similarities in GLP-1 Receptor Agonist Cardiovascular Outcomes Trials.” *Trends in endocrinology and metabolism: TEM* vol. 30,9 (2019): 578-589.
Ryan, D. and Acosta, A. (2015), GLP-1 receptor agonists: Nonglycemic clinical effects in weight loss and beyond. Obesity, 23: 1119-1129

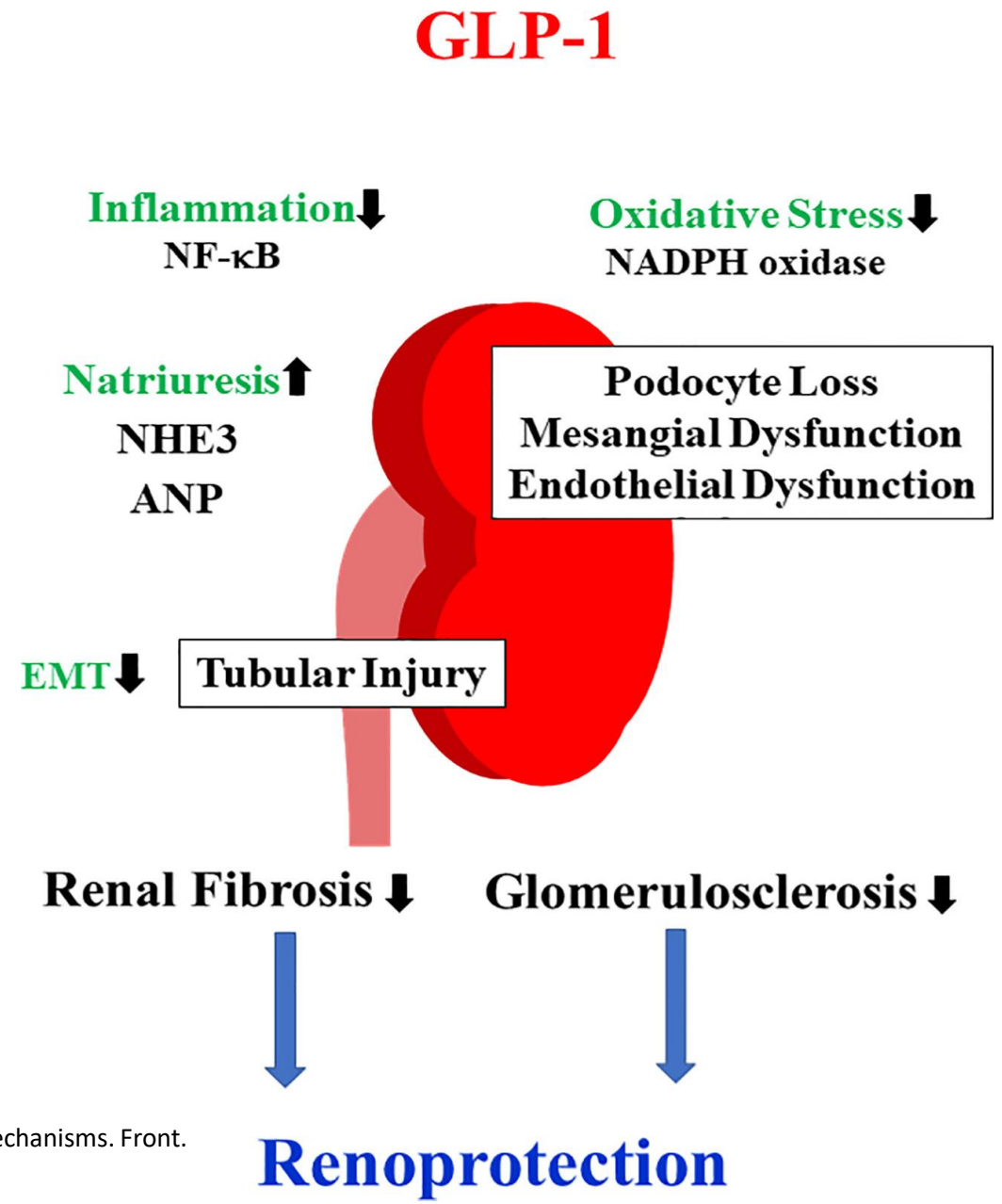
GLP-1RA and CVD



Daniel Drucker. The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metabolism. Volume 24, Issue 1, 12 July 2016, Pages 15-30

GLP-1RA and Renoprotection

- Increases naturesis and diuresis
- Decreases inflammation and oxidative stress
- Decreases renal fibrosis and glomerulosclerosis
- Decreases risk of diabetic nephropathy
- There is satisfactory evidence demonstrating treatment with GLP-1RA reduces albuminuria



Kawanami D. GLP-1 Receptor Agonists in Diabetic Kidney Disease: From Clinical Outcomes to Mechanisms. Front. Pharmacol., 30 June 2020

Greco EV, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 Receptor Agonists and Kidney Protection. *Medicina (Kaunas)*. 2019;55(6):233.

GLP-1RA and Metabolic Associated Fatty Liver Disease

- The incidence of metabolic associated fatty liver disease (MAFLD) is increasing. First line treatment is lifestyle intervention for weight loss of 5-10%, but most patients do not achieve or maintain.
- No pharmacotherapy for MAFLD has been approved
- Recent animal studies indicate that GLP-1RAs can reduce liver inflammatory lesions and even slow the process of steatosis change into fibrosis.
- A systematic review and meta-analysis looked at eight randomized controlled trials including 396 patients (265 patients had type 2 diabetes).
- GLP-1RA group showed significant reduction in liver fat content, body weight, waist circumference, ALT, GGT, fasting blood glucose, and hemoglobin A1c.
- GLP-1RA may improve liver injury and metabolic disorder in patients with metabolic associated fatty liver disease

Dai Y, He H, Li S, et al. Comparison of the Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Patients With Metabolic Associated Fatty Liver Disease: Updated Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2021;11:622589. Published 2021 Feb 16.

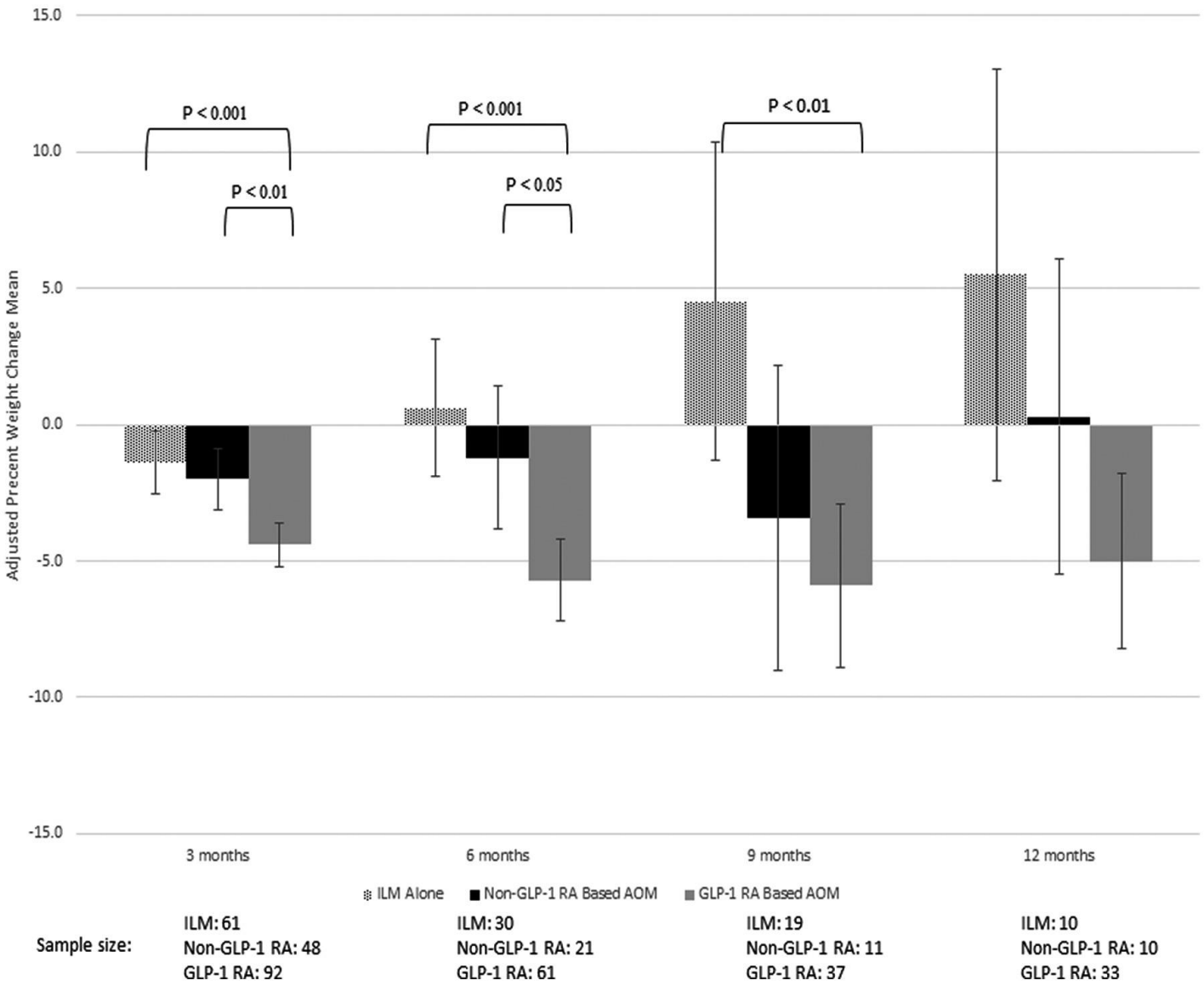
GLP-1RA and Taste Perception Changes

- GLP1 receptors are expressed in taste buds
- Recent studies show that GLP-1RA decreases brain responses to anticipation of palatable food while increasing response to actual receipt of palatable food, leading to decreased intake.
- Liraglutide affects appetite regulation through action on GLP1 receptors in the parietal lobe, insula, and putamen, suggesting how activation of GLP1 receptors may counteract cravings and overeating.
- Dulaglutide decreases binge eating behavior in T2DM

Da Porto et al. Dulaglutide reduces binge episodes in type 2 diabetic patients with binge eating disorder: A pilot study. Diabetes & Metabolic Syndrome: Clinical Research & Reviews Volume 14, Issue 4, July–August 2020, Pages 289-292.

GLP-1RA is More Effective in Treating Post Bariatric Weight Regain

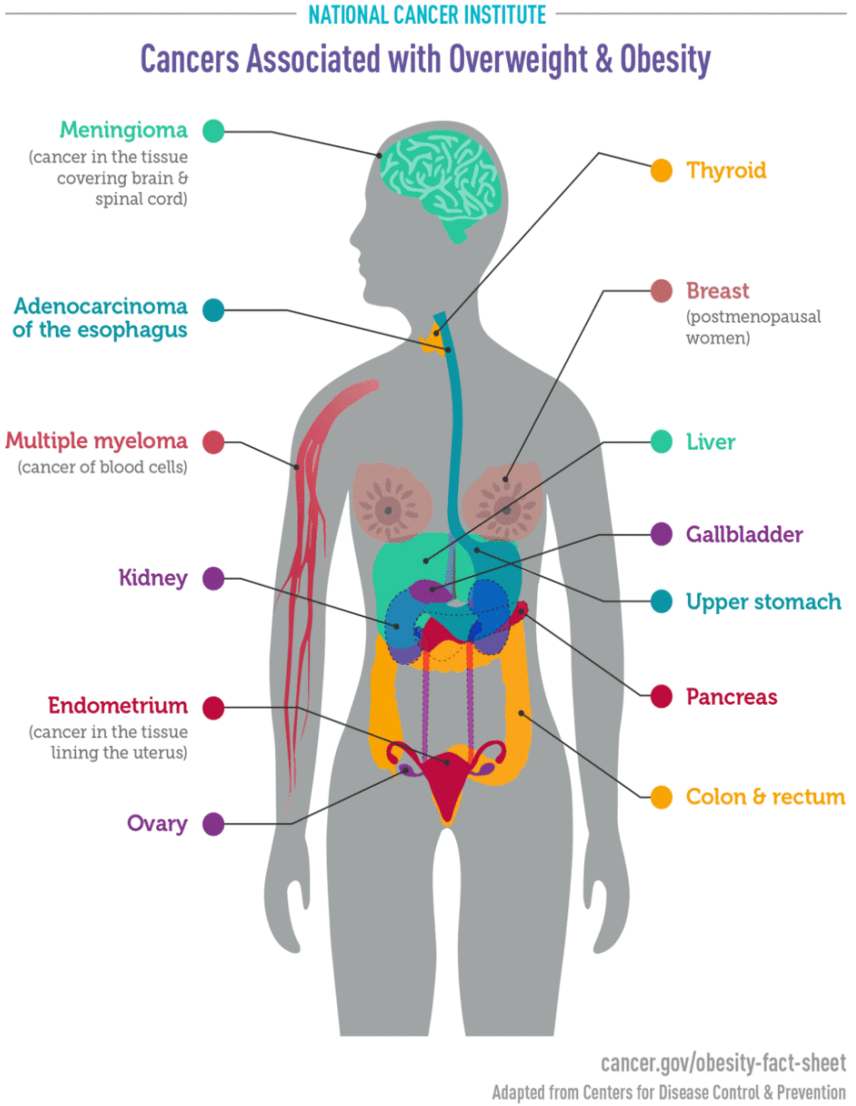
- Weight regain after bariatric surgery is a challenging issue in long-term obesity management
- This study compared real-world outcomes data of pharmacotherapies for weight regain in 207 patients with a history of sleeve gastrectomy
- Percentage body weight loss was examined in intensive lifestyle management (ILM), non-GLP1RA-based weight loss pharmacotherapy (WLP) and GLP1RA-based WLP groups
- Greatest weight loss at 3 months (4.5% ± 3.1%), 6 months (6.7%±5.5%), and 9 months (6.9%± 6.9%) was observed in the GLP1RA-based WLP group
- Notably, despite having more patients with type 2 diabetes in GLP1RA-based WLP group, this group still had the greatest weight loss at each time point.



Gazda, Chellse, Clark, John, Ildiko Lingvay, and Jaime Almandoz. "Pharmacotherapies for Post-Bariatric Weight Regain: Real-World Comparative Outcomes. Obesity, Vol 29; 5. May 2021. 829-835.

GLP-1RA on Tumor Diseases

- Obesity is linked to 16 cancers
- Hyperinsulinemia appears to be the main reason for increased risk of cancer.
- Strategies to lower insulin have the potential to slow cancer growth.
- Meta-analysis of clinical studies indicate that GLP1RA treatment of patients with obesity and type 2 diabetes **did not increase risk** of breast tumors, nor increase risk of acute pancreatitis, pancreatic cancer, and overall tumor neoplasia.
- Longitudinal data from clinical trials have not demonstrated a causal association between GLP-1 analogs and thyroid C-cell pathology over a 2-year period.



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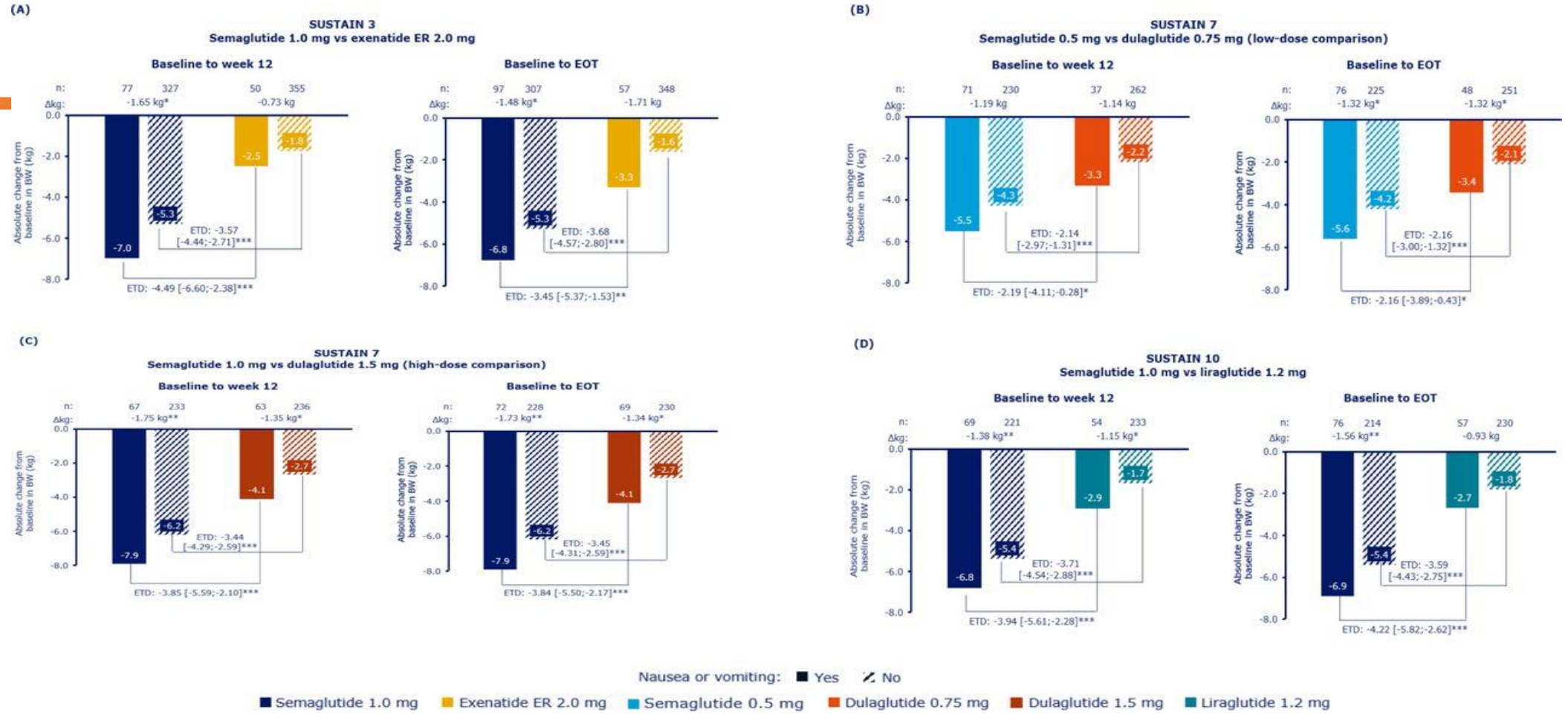
Gallagher, E.J., LeRoith, D. Hyperinsulinaemia in cancer. *Nat Rev Cancer* **20,** 629–644 (2020).

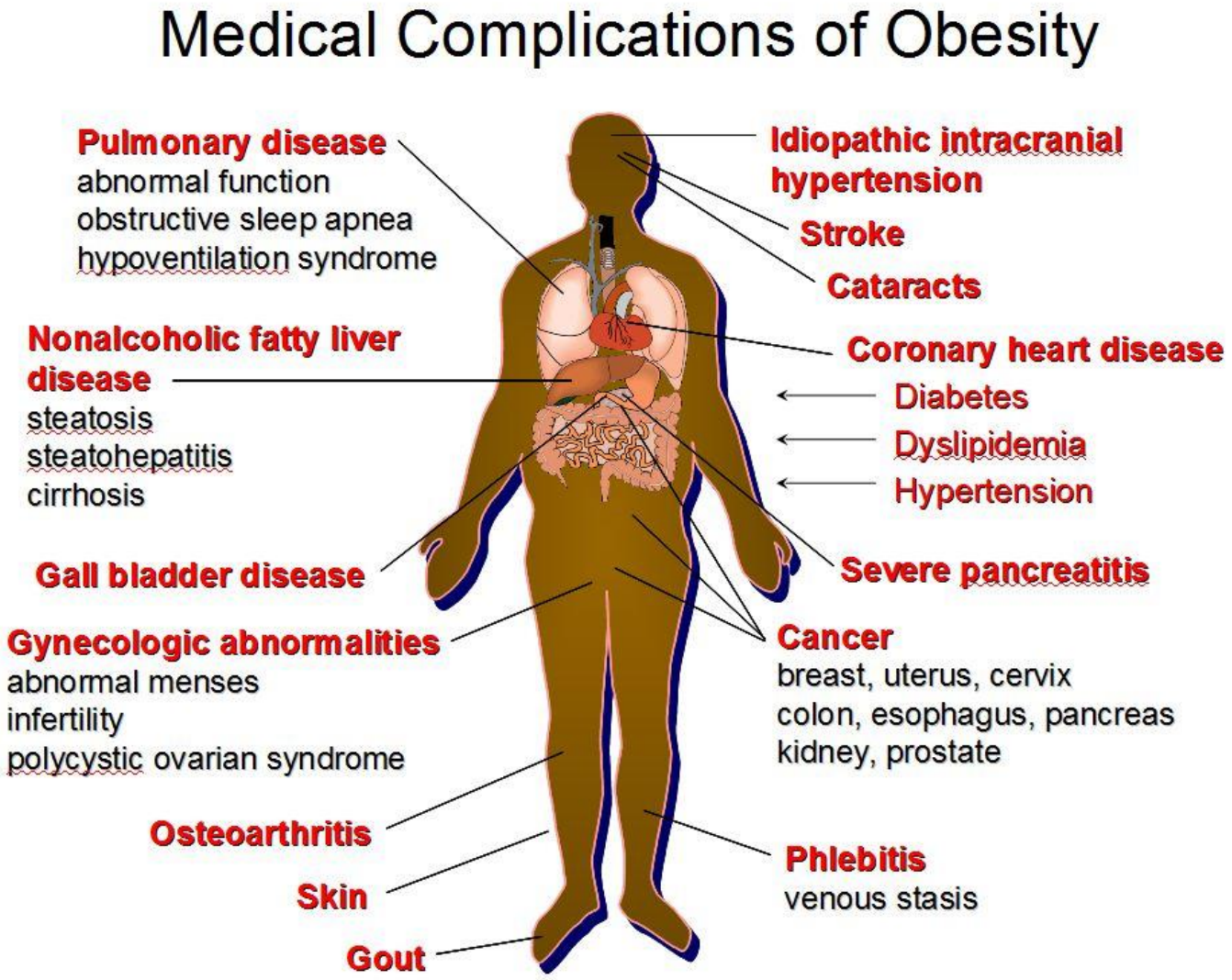
Chiu WY, Shih SR, Tseng CH. A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. *Exp Diabetes Res*. 2012;2012:924168.

Superior Weight Loss with Once-weekly Semaglutide Versus Other Glucagon-like Peptide-1 Receptor Agonists is Independent of Gastrointestinal Adverse Events.



Lingvay I, Hansen T, Macura S*, et al.* Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events. *BMJ Open Diabetes Research and Care* 2020

Treat Obesity First



GLP1-RA Monitoring

Pancreatitis – monitor for abdominal pain, nausea/vomiting. If symptoms arise, stop medication immediately. Check lipase only if symptomatic.

HR elevation /palpitations

GI side effects – nausea, vomiting, constipation, diarrhea, gallstones*

Avoid in pregnancy/ breastfeeding

- Document birth control use and counseling

Avoid in PMH or Fhx of Medullary thyroid cancer/MEN2

- only observed in rodent studies

* In clinical trials, cholelithiasis was reported by 1.6% of Wegovy™ patients and 0.7% of placebo patients. Cholecystitis was reported by 0.6% of Wegovy™ patients and 0.2% of placebo patients.

DALLAS OBESITY SOCIETY

Panel Discussion

- Dr Tonia Vinton – President, moderator
- Dr Richa Mittal – Vice President
- Susan Bowlin, NP - Treasurer
- Dr Jaime Almandoz – Trustee
- Jeff Schellinger, RD – Trustee

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