Pancreatitis, Thyroid Cancer and Ocular Problems
Side Effects of GLP-1s

W. Scott Butsch, MD, MSc FTOS

Director of Obesity Medicine | Bariatric and Metabolic Institute | Cleveland Clinic

butschw@ccf.org | drbutsch

Disclosures

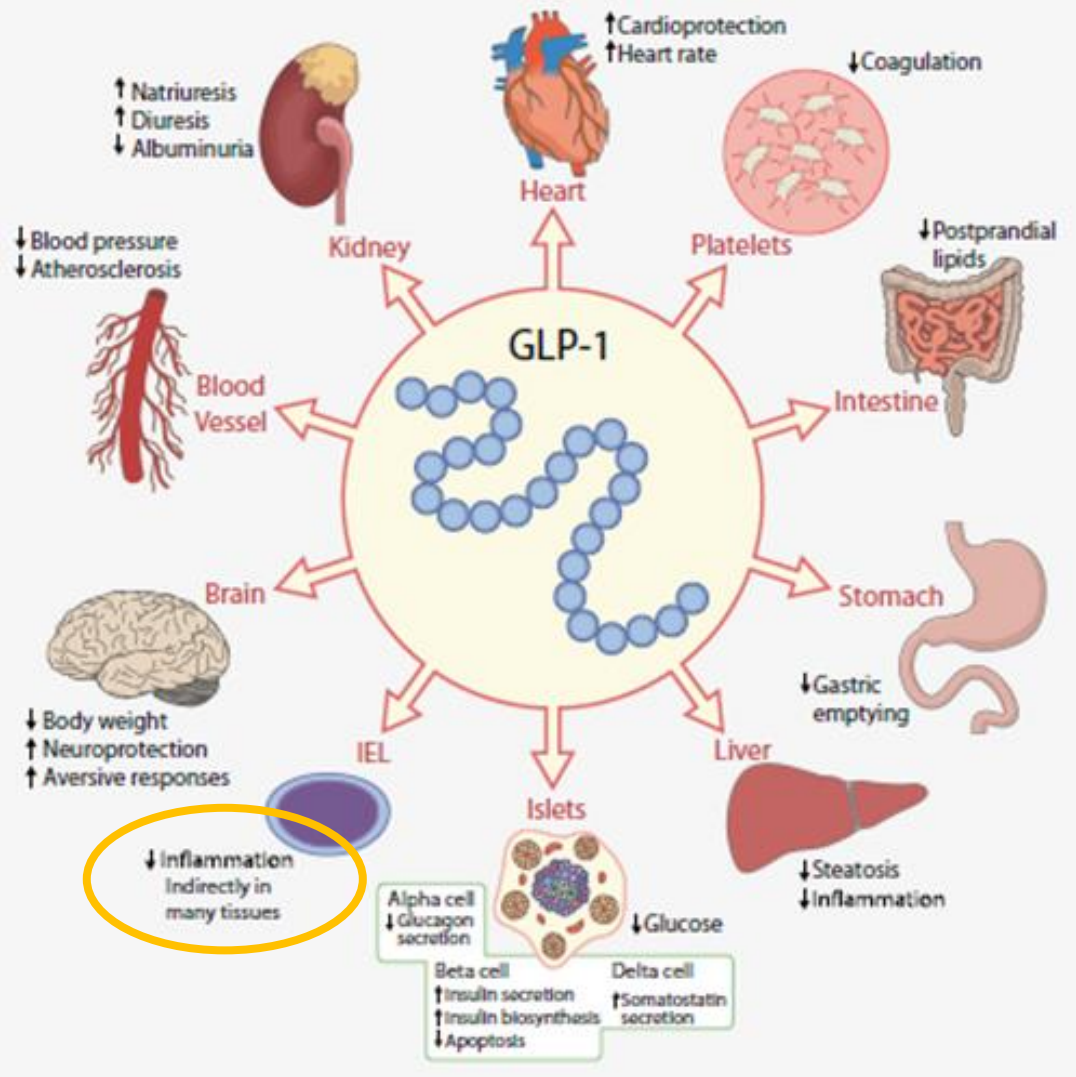
- Abbott
- Boehringer Ingelheim
- Verdiva Bio
- Novo Nordisk (*not current*)
- Eli Lilly (*not current*)

Dr Butsch anticipates discussing off label medications for obesity

Objectives

- Recognize new GLP-1 receptor agonists and emerging nutrient stimulated, hormone-based (NuSH) drugs are highly effective therapies for obesity
- Identify significant adverse effects associated with GLP1RA drugs, specifically current risks on pancreatitis, thyroid cancer and ocular problems

The Direct and Indirect Effects of GLP-1RA

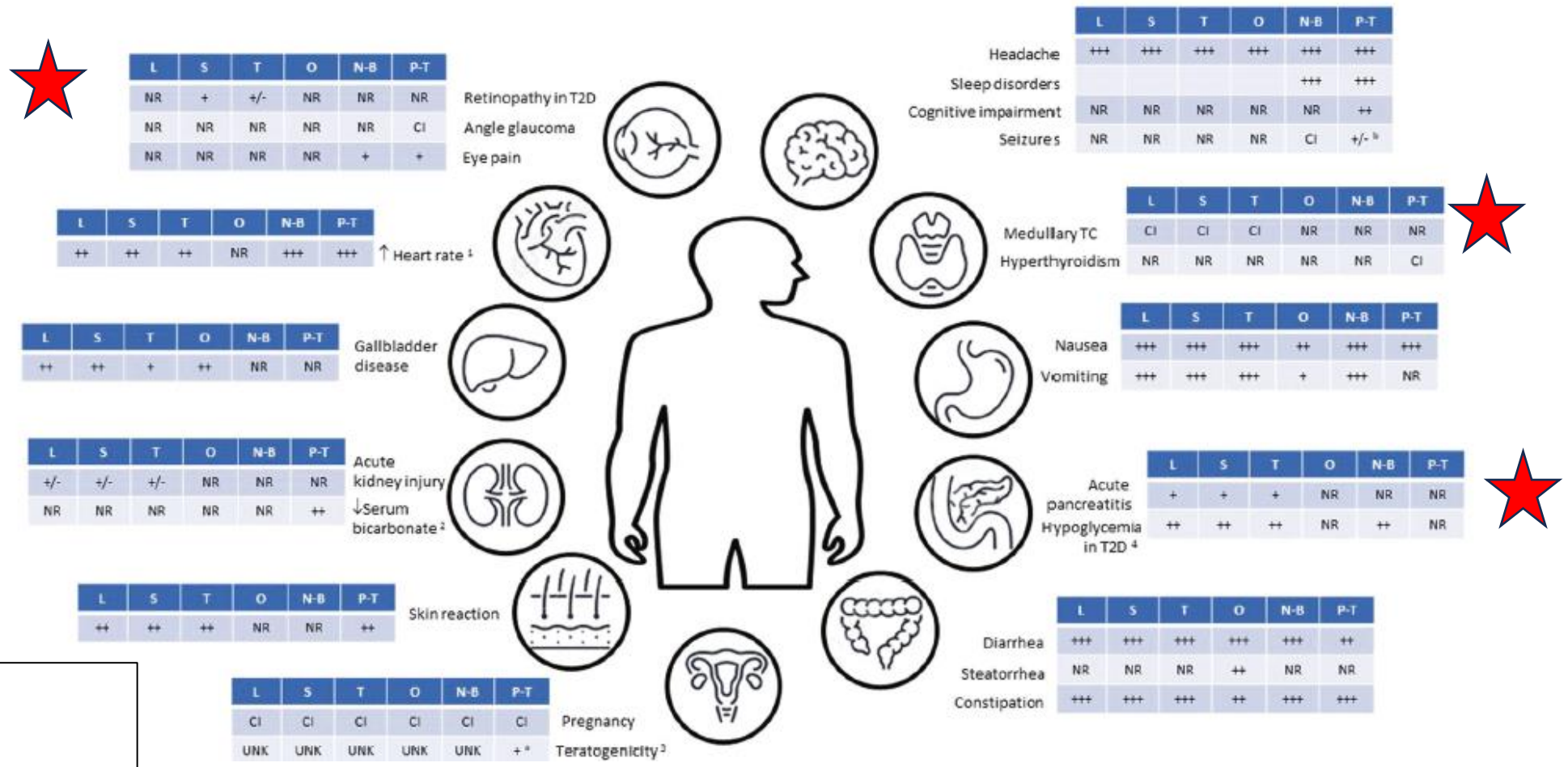


GLP-1RAs may **ameliorate inflammatory states** through a **direct mechanism**

GLP1RA benefit may be through an **indirect mechanism** by improvement of glycemic control and weight loss

Drucker DJ. *Diabetologia* 2023;66: 1765-79

Understanding Adverse Effects of GLP1s

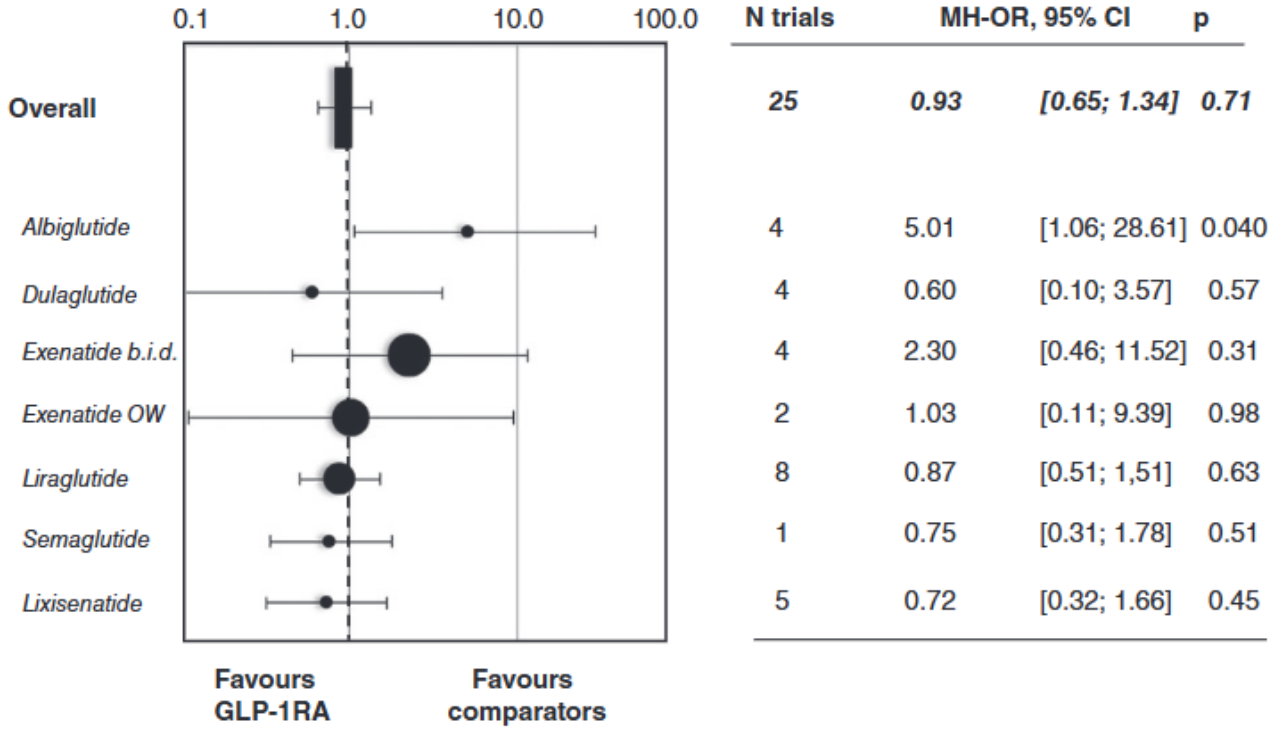


+ (>0.1-1%)
++ (1-5%)
+++ (>5%)
NR non reported
CI – contraindication
UKN unknown

Vidal et al. *Int J Obes*, 2024

Acute Pancreatitis, Pancreatic Cancer Risk

GLP-1RAs vs Comparator Drugs in T2D



	N trials	MH-OR, 95% CI		p
Overall	***25***	***0.93***	***[0.65; 1.34]***	***0.71***
Albiglutide	4	5.01	[1.06; 28.61]	0.040
Dulaglutide	4	0.60	[0.10; 3.57]	0.57
Exenatide b.i.d.	4	2.30	[0.46; 11.52]	0.31
Exenatide OW	2	1.03	[0.11; 9.39]	0.98
Liraglutide	8	0.87	[0.51; 1,51]	0.63
Semaglutide	1	0.75	[0.31; 1.78]	0.51
Lixisenatide	5	0.72	[0.32; 1.66]	0.45

N=113 trials

Pancreatitis – 28 trial (17k vs 15+k pts)
- 60 vs 55 events

Pancreatic Cancer – 15 trials (15k vs 13k)
- 24 vs 23 events

Monami M et al. *Diabetes Obes Metab*. 2017;19:1233-41

Thyroid Cancer and GLP1RA

- C-cell hyperplasia risk with GLP1RA in Rodents
  - Dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of Wistar rats and mice

- GLP1 receptors are much less expressed in humans
- Calcitonin levels have not been increased in GLP1RA RCTs in humans

Martín-Lacave et al. Cell Tissue Res. 1999;297:451

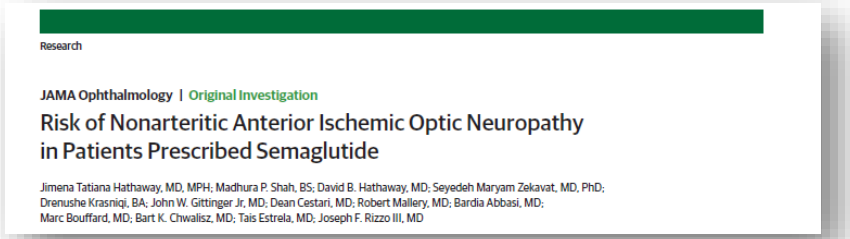
Incidence of Acute Pancreatitis and Diabetic Retinopathy in GLP1RA RCTs

	Acute Pancreatitis (% incidence)		Diabetic Retinopathy
	Drug	Placebo	
SCALE (liraglutide)	0.3	0.1	No Reports
STEP (semaglutide)	0.2	0.1	4%, 2.7%, and 2.7%, (2.4mg,1.7mg, P)
SELECT (semaglutide)	0.2	0.3	+
SURMOUNT (tirzepatide)	<0.3	<0.3	< 1%, 0%, and < 1% (10 mg, 15 mg, P)

****Higher** doses of **Semaglutide** (**8mg, 16mg**) in T2D– **no differences vs Placebo – Acute Pancreatitis, Diabetic Retinopathy**

Aroda VR et al. *Diabetes Care* 2025;48(6):905-13

Association of nonarteritic anterior ischemic optic neuropathy (NAION) with Semaglutide


Research

JAMA Ophthalmology | Original Investigation

Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

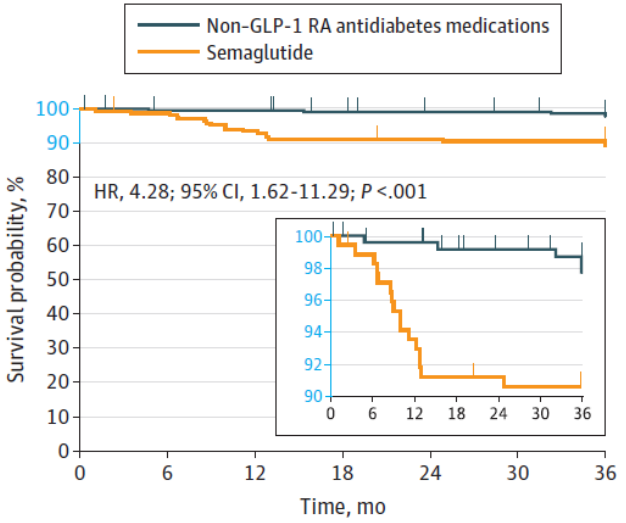
Jimena Tatiana Hathaway, MD, MPH; Madhura P. Shah, BS; David B. Hathaway, MD; Seyedeh Maryam Zekavat, MD, PhD; Drenushe Krasniqi, BA; John W. Gittinger Jr, MD; Dean Cestari, MD; Robert Mallery, MD; Bardia Abbasi, MD; Marc Bouffard, MD; Bart K. Chwalisz, MD; Tais Estrela, MD; Joseph F. Rizzo III, MD

JAMA Ophthalmol. 2024;142(8):732-739.

Retrospective matched cohort, 2017-23
N=16837, Rx Sema vs non-GLP1RA, in T2D, Obesity
Primary Endpoint: nonarteritic anterior ischemic optic neuropathy (NAION)

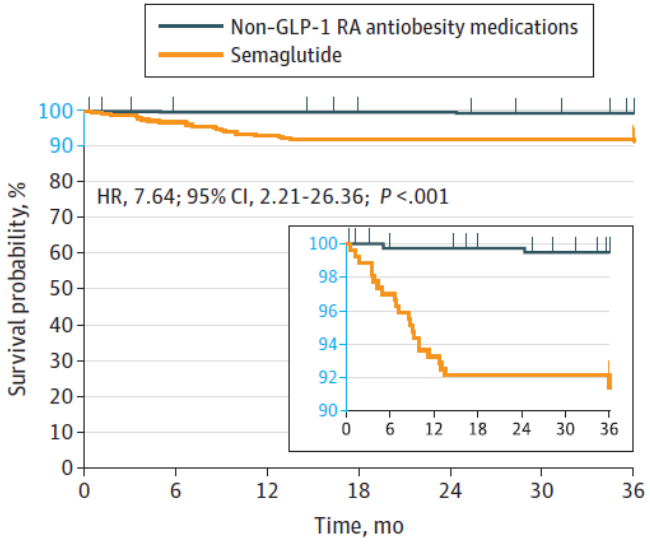
N=710
17 (8.9%) in sema
6 (1.8%) in other

8.9% in sema
1.8% in other



No. at risk							
Non-GLP-1 RA antidiabetes medication	234	228	228	224	221	219	181
Semaglutide	169	166	157	154	153	152	130

N=369 and 979
20 in sema
3 in other



No. at risk							
Non-GLP-1 RA antiobesity medication	359	356	356	353	352	350	301
Semaglutide	254	246	240	237	236	236	221

Summary

- **Lack of evidence to support a causal role** of GLP1RA and pancreatitis or pancreatic cancer in patients with obesity
- **No** influence of GLP1RAs on thyroid in humans, outside of adjusting thyroid hormone if needed in those with hypothyroidism
- Patients with **diabetic retinopathy may worsen** as glucose levels improve with weight loss but its unclear that GLP1RA medications are causal
- Ocular disorders eg NIAON appear to be associated with GLP1RAs in some studies, however data is unclear and causal role is not known.

Take Home Points

- Start with **low dose** of OMMs
- Monitor weight and for adverse effects, especially **with dose escalation**
- More caution in those individuals with **h/o unknown pancreatitis**
- **Don't take the patients word** about non-MTC, MEN2 - obtain the medical records
- May use in those with h/o **other types of thyroid cancer** (eg follicular) but CONTRAINDICATED in MEN2 and MTC
- Educate patients to **communicate** if any new ocular changes, especially in those with diabetes