GLP-1 Side Effects

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Mechanism Of Action

- GLP-1 is produced in L cells of small intestine in response to food intake
- Stimulates glucose-dependent insulin release
- Slows gastric emptying
- Inhibits post meal glucagon.

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Common Side Effects

- Nausea
- Vomiting
- Diarrhea
- Up to 50% of patients
- Increased risk during dose escalation
- Usually improves over time.

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Common Side Effects

- Reassess symptoms prior to starting- missed gastroparesis
  - Incidence 6.3 per 100,000 person years
  - Approx 50% idiopathic
- Do not do gastric emptying study on GLP-1 RA

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https://www.uptodate.com/contents/gastroparesis-etiology-clinical-manifestations-and-diagnosis?search=gastroparesis&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2#H2

GI S/E Mitigation Strategies

- Education on MOA and side effects prior to initiation
- Eat slowly and smaller portions
- Stop eating at 1st sensation of fullness.
- Avoid meals with increased amounts of fat
- Food diary to isolate offending foods.
- Slower titration

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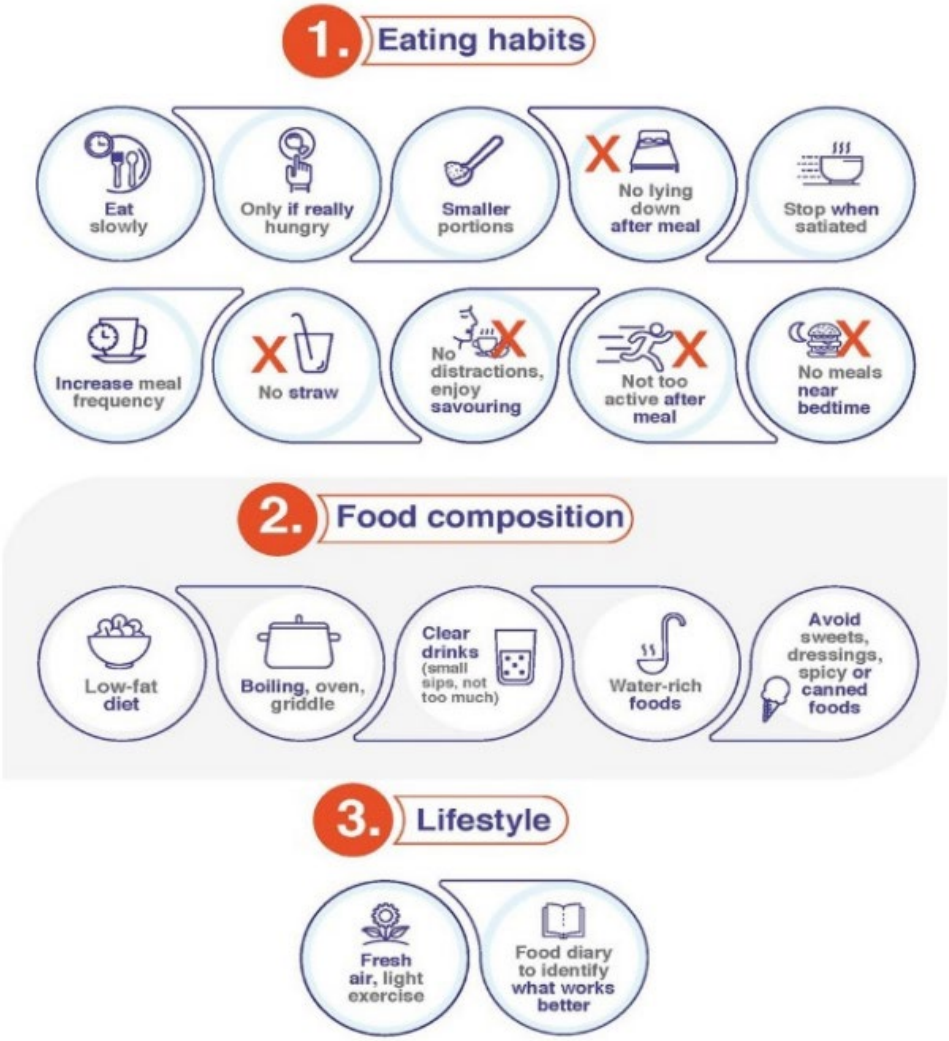
Gorgojo-Martinez et al. J Clin Med. 2023,12 145.

GI S/E Mitigation Strategies



Gorgojo-Martinez et al. J Clin Med. 2023,12 145.

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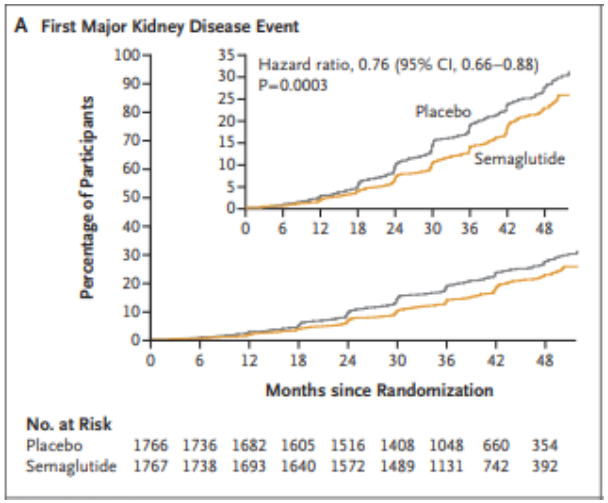
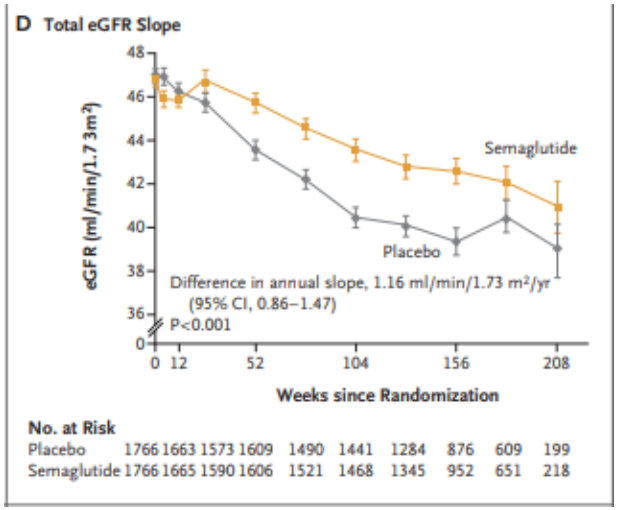
Renal

- Dehydration due to GI s/e.
- GLP-1 Study on 24 water intake with or without food.
  - GLP-1 have a hypodipsic effect through CNS GLP receptor activation.
- FLOW trial





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Mckay et al. AM J Phys Reg Integ Comp Phys. 2011 Oct 5; 301 (6)
Perkovic et al. NEJM. 2024; 391:109-121

Pancreas/Gallbladder

- Unclear association between pancreatitis and GLP-1
- Diabetes is a risk factor for pancreatitis
- GLP-1 does increase amylase so amylase should not be checked routinely
  - GLP receptors in acinar cells that make amylase
- No Receptors in the pancreatic ducts.
- GLP-1 may reduce inflammation in pancreas
- Conflicting evidence on pancreatitis risk
- Avoid use in history of pancreatitis

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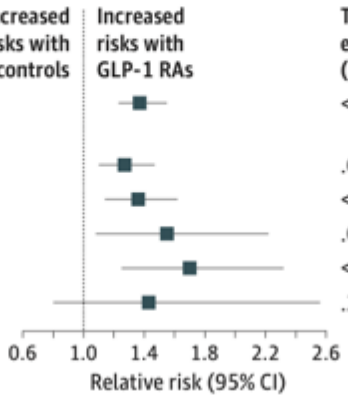
Pancreas/Gallbladder

- GLP-1 known to increase risk of gallstones.
- Also assoc with rapid weight loss- bariatric surgery
  - 20.7% had gallbladder disease (8.2% symptomatic)
- Meta analysis of 76 RCT

Figure 2. Risks of Cholelithiasis, Cholecystitis, and Biliary Diseases in Patients Randomized to GLP-1 RA Treatment Compared With Controls in All Trials

Outcomes	No. of studies	No. of events/total: GLP-1 RAs groups	No. of events/total: Control groups	ARD (95% CI) per 10 000 persons/year	I^2, % (95% CI)	Relative risk (95% CI)	Test of effect (*P* value)	Q test (*P* value)
Gallbladder or biliary disease	76	916/57 856	544/45 515	27(17 to 38)	0 (0-27)	1.37 (1.23-1.55)	<.001	.86
Cholelithiasis	61	454/53 674	287/42 212	14 (5 to 24)	0 (0 to 30)	1.27 (1.10 to 1.47)	.001	.99
Cholecystitis	53	302/49 491	187/40 574	10 (4 to 18)	0 (0 to 32)	1.36 (1.14 to 1.62)	<.001	.99
Biliary disease	21	77/36 225	41/32 741	2 (0 to 5)	0 (0 to 48)	1.55 (1.08 to 2.22)	.02	.99
Cholecystectomy	7	125/13 690	61/11 479	9 (3 to 17)	0 (0 to 71)	1.70 (1.25 to 2.32)	<.001	.49
Biliary cancer	12	25/31 010	15/30 026	5 (-3 to 20)	0 (0 to 58)	1.43 (0.80 to 2.56)	.22	.86



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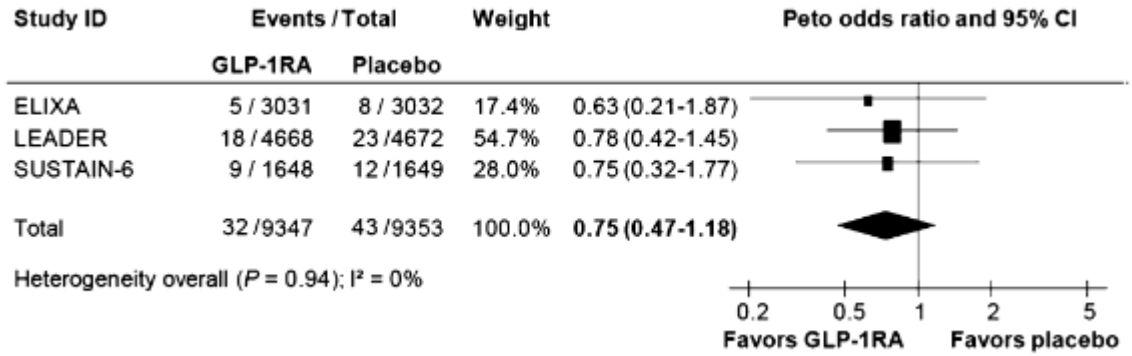
Amorim-Cruz et al. J Gastro Surg 2023; 27 (2): 433
Liyun eta al, JAMA IM 2022; 182 (5): 513-19

Pancreas/Gallbladder

- Meta Analysis acute pancreatitis in Type 2 Diabetes- ELIXA, LEADER, SUSTAIN-6



- Meta Analysis looking at Biliary Disease

Table. Factors and Risks of Gallbladder or Biliary Diseases in 76 Randomized Clinical Trials of GLP-1 RA Drug Use

Factor	No. of patients	No. of trials	Relative risks (95% CI)	Heterogeneity I^2 %	Heterogeneity P value	P value for interaction[a]
Treatment						
Dose[b]						
High	61 962	54	1.56 (1.36-1.78)	0	.99	.006
Low	16 952	33	0.99 (0.74-1.33)	0	.67	
Duration, wk						
≤26	13 401	24	0.79 (0.48-1.31)	0	.97	.03
>26	90 417	53	1.40 (1.26-1.56)	0	.64	

Storgaard et al. Diab Obes Met 2017; 19:906-908
He et al. JAMA Int Med May 2022; Vol 182. # 5

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Thyroid Cancer

- Current black box warning for Medullary Thyroid Cancer and MEN 2
  - Cancer of the thyroid parafollicular or C cells.
  - 1-2% of all thyroid cancers
  - C-cell tumors seen in rodent studies
  - Rodents have > C cells and greater GLP-1 expression
  - Calcitonin does not need to routinely checked prior to starting or monitored
- MEN 2- MTC, parathyroid disease, Pheochromocytoma
- No contraindication for other thyroid cancer or patients with thyroid nodules.

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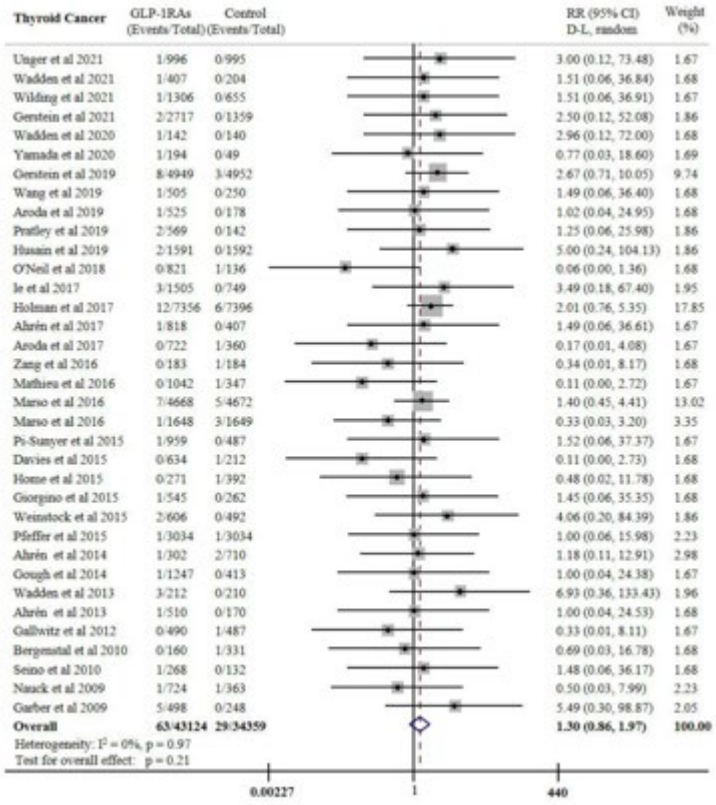
Thyroid Cancer

- Meta Analysis 45 trials
  - No assoc between GLP-1 and thyroid cancer



Hu et al. Front Endocrinology, July 10, 2022

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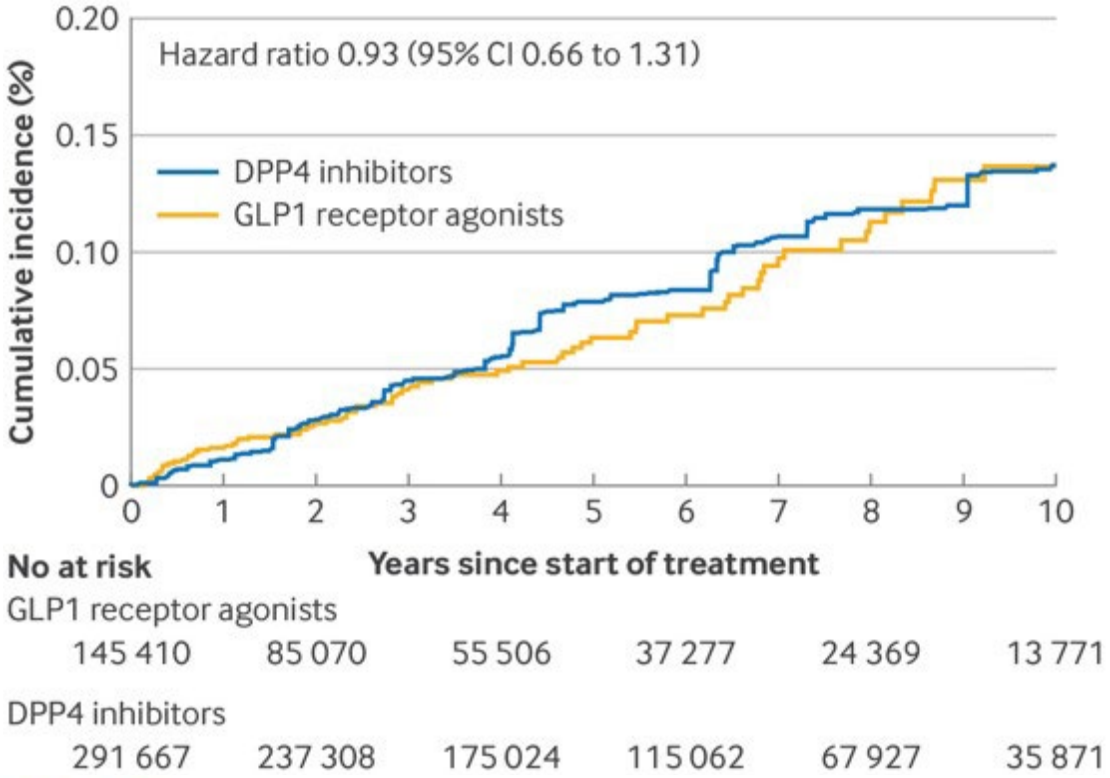
Thyroid Cancer

- Scandinavian Cohort study
- DPP-4 vs GLP-1



Pasternak et al. BMJ; 2024;385

Gastric Emptying

- Known MOA of GLP-1
- Do not use in patients with gastroparesis
- No data for long term gastric paralysis
- If planning on surgery- Previous anesthesia statement is to hold GLP-1 the week prior for LA GLP-1
  - Expert opinion as opposed to a data driven recommendation
- ½ life of LA GLP-1- 1 week
- 2024 Multi society Guidance
  - Shared Decision making- Patient, anesthesia, prescribing team.
  - Minimize asp risk if GLP-RA used- Ex: preop liquid diet 24 hrs, gastric US
- Work with local surgery and anesthesia team

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Kindel et al. Surg for Obes and Rela Dis 20 (2024); 1183-1186

Post op Aspiration Pneumonia

- Retrospective cohort study
- Claims database
- Looked at 14 common surgeries
- Exclusion- < 18 yo, Multiple surgeries, or Hx of pneumonia within 90 days.
- 5931/366,476 pt on GLP-1 RA
- No Difference in post op pneumonia
  - OR 0.78 with a P=.12

Surgical procedure
Bariatric surgery
Knee arthroplasty
Hip arthroplasty
Colectomy
Laminectomy
Spinal fusion
CABG
Groin hernia repair
Thyroidectomy
Hysterectomy
Lower extremity amputation
Appendectomy
Hip fracture (femoral, intertrochanteric)
Tibial and ankle shaft fractures

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Chen et al. JAMA, 2025;8(3)

Vision

- Nonarteric Ant Ischemic Optic Neuropathy (NAION)
  - Single center, semaglutide- retrospective 36 months
  - Ischemic event of optic nerve head- acute ischemia
  - Mainly older adults
  - 2-10/100,000 persons
  - Assoc risk factors: atherosclerosis, nocturnal hypotension, thrombotic risk
  - 710/16,827 with DM 2 (194 Rx for Sema)
  - 979 obese (361 Rx sema)
  - NAION: Sema 8.9% vs Non GLP 1.8%
  - Obesity: 20 events (Sema) vs 3 in Non GLP

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Hathaway et al. JAMA ophth, published July 3, 2024

NAION

- Retrospective study
- Global database looking at DM 2 or obese
  - 37 K- Diabetes only
  - 129 K obesity only
  - 130K Diabetes and obesity
- No association with semaglutide and increased rates of NAION

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Chou et al. Ophthalmology, 2025 Aprl; 132 (4): 381-388

Vision

- Diabetic retinopathy
- SUSTAIN 6- Semaglutide CVO Trial
- Increased rate of retinopathy complications.
- 50 (3%) in Sema vs 29 (1.8%) in Placebo- HR 1.76
- Rapid A1c improvement Assoc with worsening retinopathy
- FOCUS Trial- PENDING
  - Semaglutide effect on retinopathy
  - 5 yr study

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Marso et al. NEJM 2016; 375: 1834-1844

Suicide Risk

- Case Reports of suicide
- FDA: Did not find assoc with GLP-1 and suicide risk. Continuing to monitor.
- EMA: Available evidence does not support causal assoc between GLP-1 and suicidal thoughts and actions
- Assoc with Bariatric Surgery and Suicide
  - 2.7 vs 1.2 per 10,000 patient years

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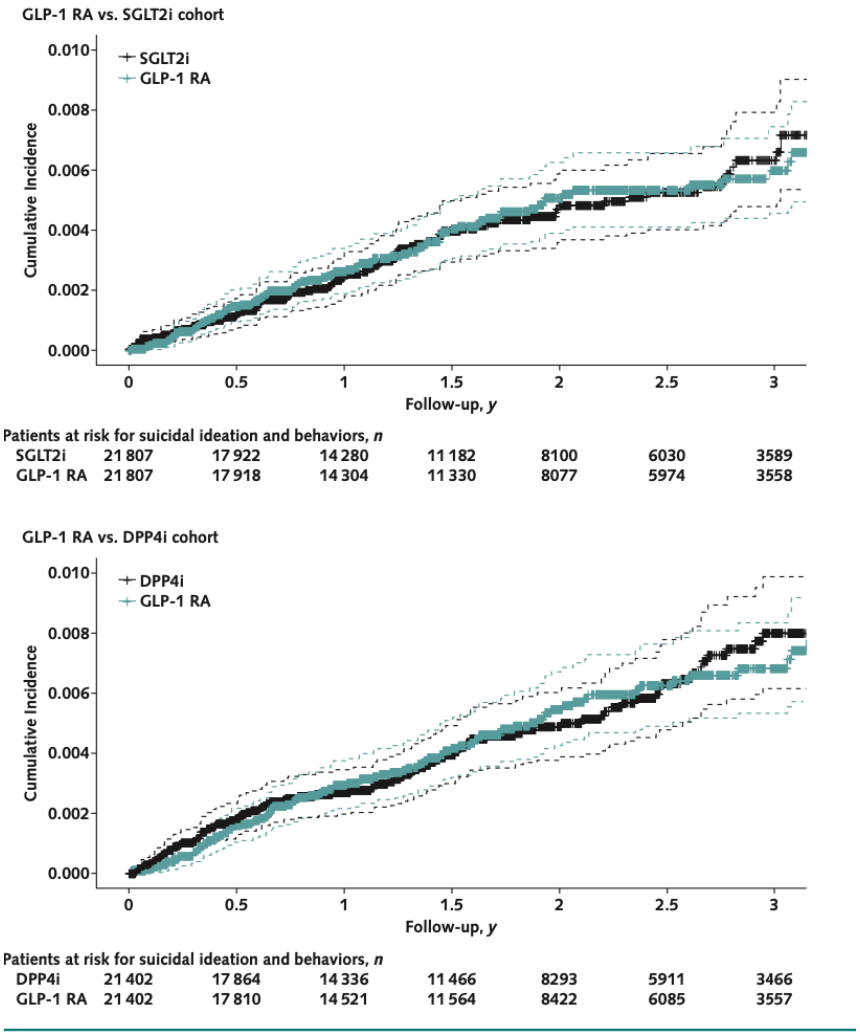
Adams et al NEJM. 2007; 357 (8):753

Suicide Risk

- Retrospective review based on ICD codes
- GLP-1 vs SGLT 2 vs DPP 4
- Age ≥ 66 with DM 2



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Tang et al. Annals of Int Med. Juy 16, 2024

Suicide Risk

- Cohort 1- 36,082 patients- GLP-1 or DPP 4
- Cohort 2- 234,028 patients- DPP 4 or SGLT 2
- UK data

Table 3 | Hazard ratios for suicidal ideation, self-harm, and completed suicide comparing glucagon-like peptide-1 (GLP-1) receptor agonists with dipeptidyl peptidase-4 (DPP-4) inhibitors

Exposure	No of patients	Events	Person years	Crude IR*	Weighted IR (95% CI)* †	Crude HR (95% CI)	Weighted HR (95% CI)†
Primary composite outcome‡							
DPP-4 inhibitors	234 028	1087	599 271	1.8	3.7 (3.6 to 3.9)	1.00 (reference)	1.00 (reference)
GLP-1 receptor agonists	36 082	301	77 337	3.9	3.9 (3.5 to 4.4)	2.08 (1.83 to 2.36)	1.02 (0.85 to 1.23)
Suicidal ideation							
DPP-4 inhibitors	234 028	679	599 987	1.1	2.4 (2.3 to 2.6)	1.00 (reference)	1.00 (reference)
GLP-1 receptor agonists	36 082	192	77 504	2.5	2.5 (2.1 to 2.6)	2.15 (1.83 to 2.53)	1.00 (0.79 to 1.26)
Self-harm							
DPP-4 inhibitors	234 028	464	600 374	0.8	1.7 (1.6 to 1.8)	1.00 (reference)	1.00 (reference)
GLP-1 receptor agonists	36 082	129	77 604	1.7	1.7 (1.4 to 2.0)	2.06 (1.69 to 2.50)	0.94 (0.70 to 1.25)
Completed suicide							
DPP-4 inhibitors	234 028	26	601 196	0.04	0.1 (0.07 to 0.1)	1.00 (reference)	1.00 (reference)
GLP-1 receptor agonists	36 082	6	77 807	0.08	0.1 (0.03 to 0.2)	1.72 (0.71 to 4.18)	0.77 (0.19 to 3.03)

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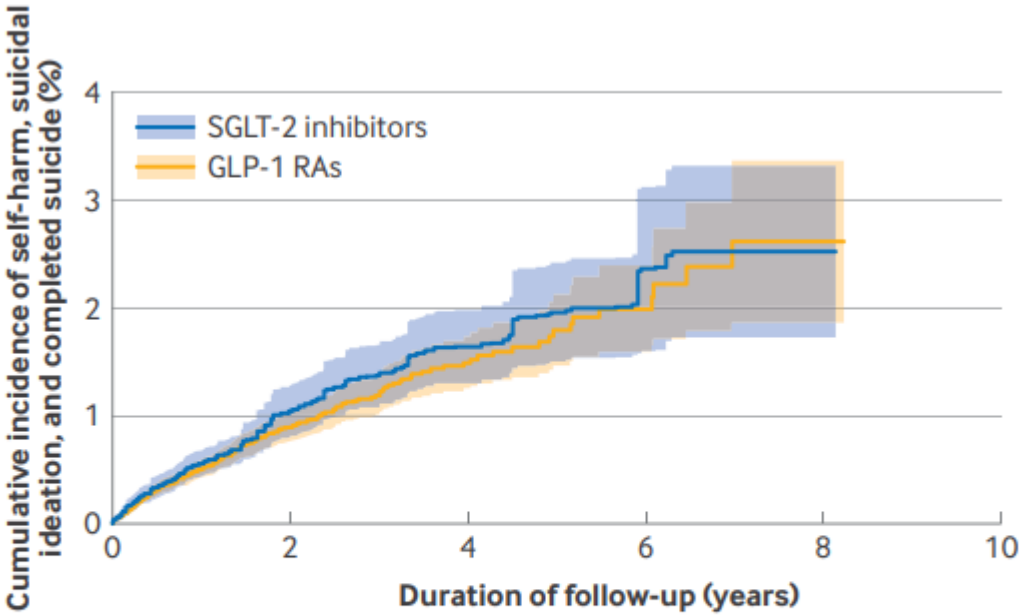
Shapiro et al BMJ 2025; 388

Suicide Risk



No at risk

SGLT-2 inhibitors	96 212	34 594	14 526	5129	90
GLP-1 RAs	32 336	9851	3157	879	86

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Shapiro et al BMJ 2025; 388

Sarcopenia

- Weight loss = Body fat loss + muscle loss.
- Review diet intake- protein intake
- Review exercise routine and encourage resistance training
- Unclear how clinically significant

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From: **Is Weight Loss–Induced Muscle Mass Loss Clinically Relevant?**

JAMA. 2024;332(1):9-10. doi:10.1001/jama.2024.6586

Figure Legend:

Body Composition Before and After Weight LossRepresentation of body composition before and after 25% intentional weight loss induced by energy restriction showing the attenuation of weight loss–induced reduction in fat-free mass (FFM) and skeletal muscle mass (SMM) through dietary protein and exercise (A) and the effect of marked weight loss induced by GLP-1–based antiobesity medications on the proportion of total weight lost derived from fat mass and lean body mass (LBM) or FFM (B). Data are from C Harris et al, J Rosenstock et al, JPH Wilding et al, and AM Jastreboff et al.

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Lean Body Mass

- DXA based assessment of LBM
- 659 pt from 9 trials.
- F/U 12-72 weeks
- 75% female
- Mean age 41.7
- BMI 30-43
- Results
  - GLP-1 RA assoc with -6.9 kg TBW
  - GLP-1 RA assoc with -1.9 kg Lean mass
  - 30% of body weight loss is lean mass

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Beavers et al. Obesity. 2025; 225-237

Glucose Lowering Treatment and Activity levels

- Pool of 3 randomized trials
- Accelerometer assessed physical activity
- Empagliflozin, Liraglutide, Sitagliptin, dietary therapy
- Lira: - 1144 steps
- Empa: - 1132 steps
- Sita: - 852 steps
- P <0.01
- Mod-Vigorous activity reduced
- Dietary intervention led to No change or increase in physical activity

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Yates et al. Diabetes Care, Aug 19, 2022

Weight Gain After Stopping GLP-1

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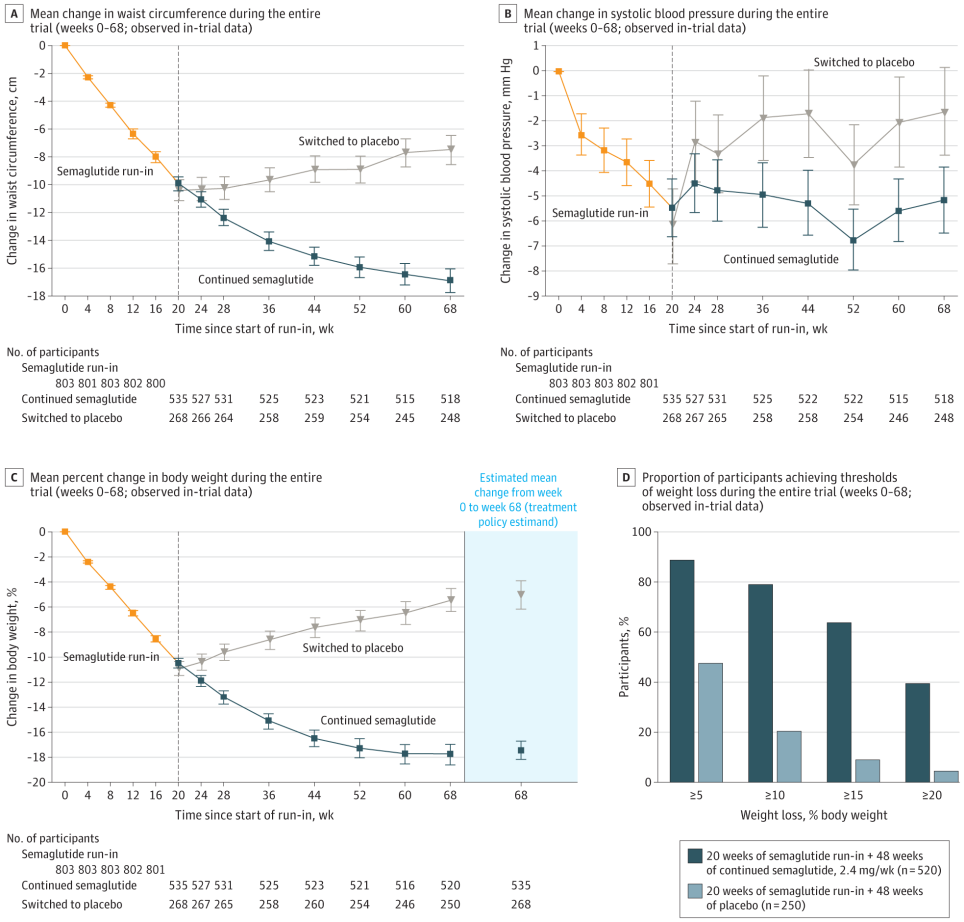
JAMA Network™

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



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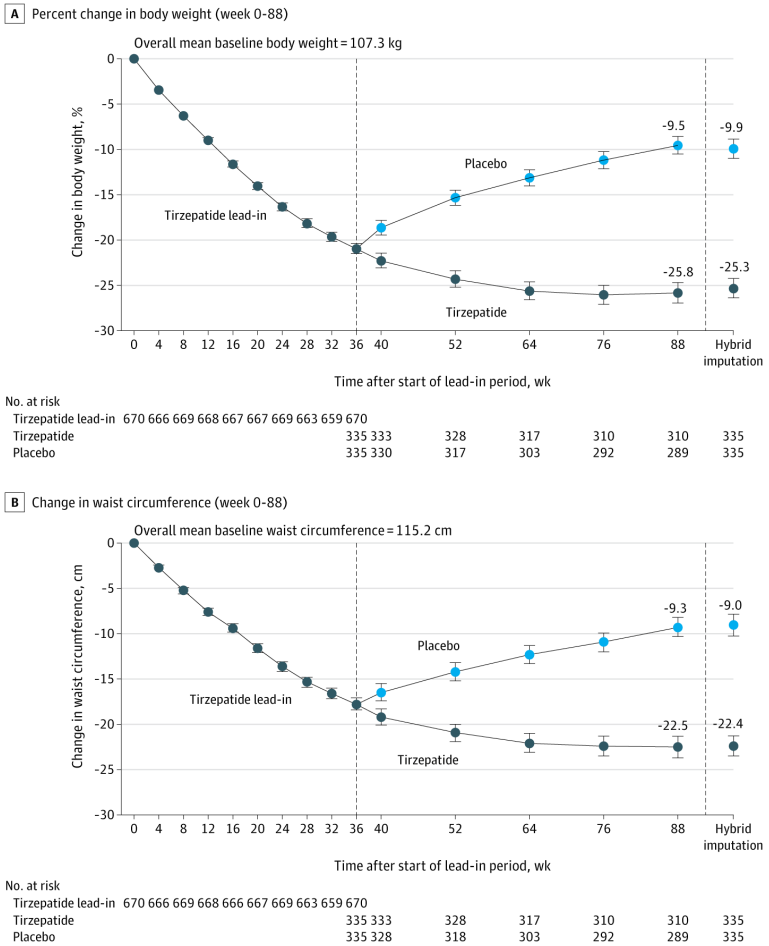
JAMA Network™

From: **Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial**

JAMA. 2024;331(1):38-48. doi:10.1001/jama.2023.24945



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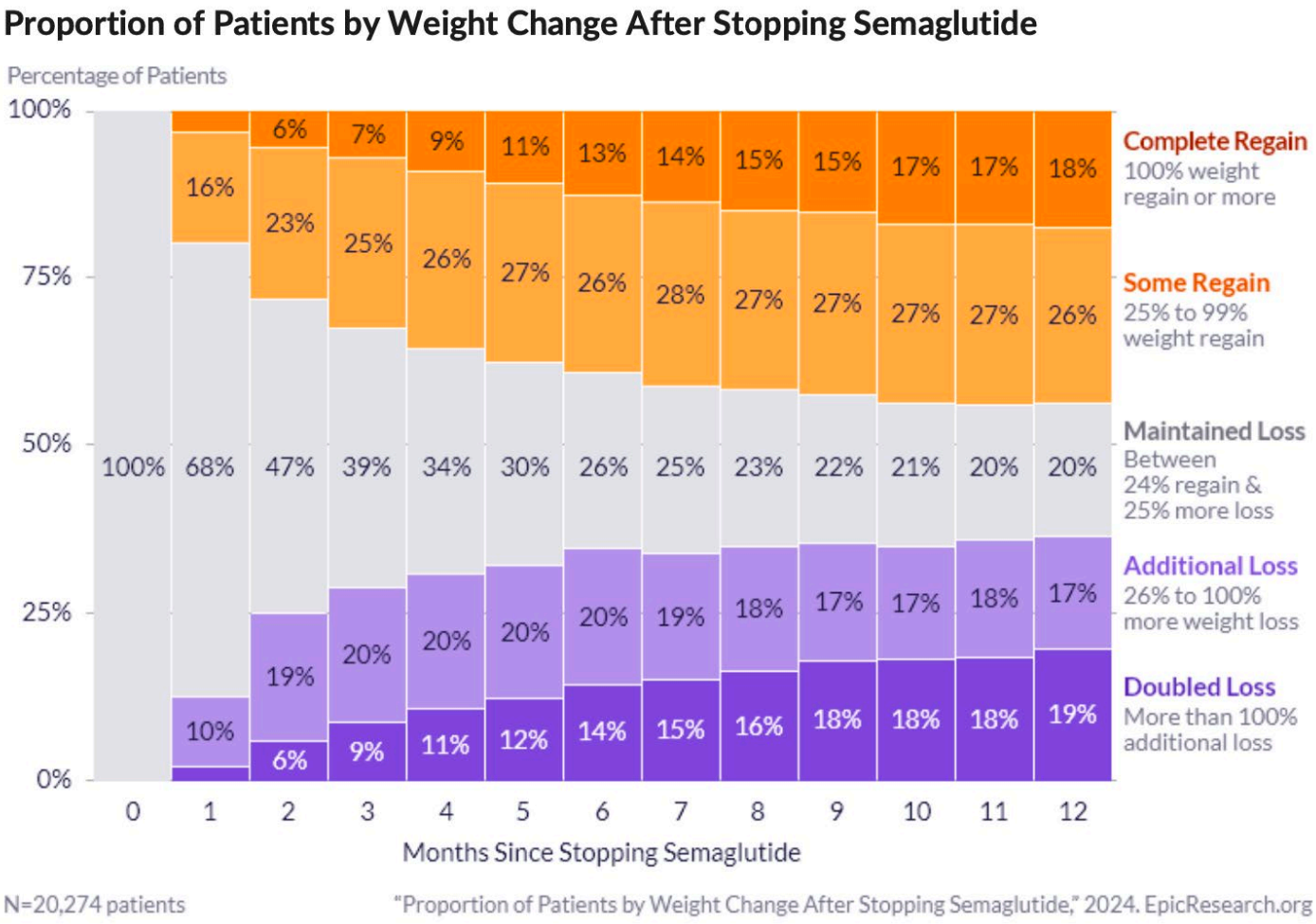
Epic Research Data



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Bartelt et al. Epicresearch.org; Jan 23 2024

Assessment When Starting GLP-1

- Titrate slowly to prevent nausea
- Stay hydrated
- Assess prior to starting potential symptoms of gastroparesis
- Do not need to monitor amylase/lipase
- Encourage resistance exercise and protein intake
- Assess behavioral health
- Assess for personal and family history of MTC or MEN 2
- Advise prior to starting that may need GLP-1 indefinitely-similar to HTN and lipid medication

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Questions

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