NEW YORK SOCIETY FOR GASTROENTEROLOGY & ENDOSCOPY
48th Annual
NEW YORK COURSE
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NYSGE
New York Society for Gastroenterology and Endoscopy

# Ramifications and implications on GLP-1 based therapies

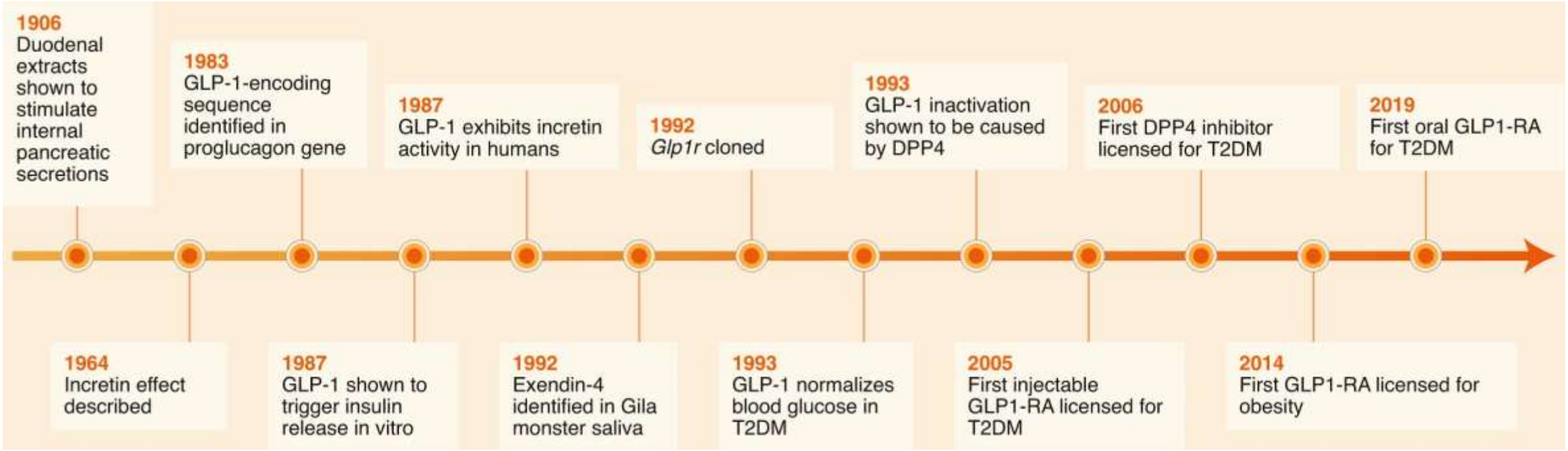
Sydney Pomenti, MD
Assistant Professor of Medicine
Columbia University Medical Center

No relevant Disclosures

# Objectives

- Discovery
- Mechanisms of Action
- Creating GLP-1 agonists
- Landmark Studies
- Efficacy & Safety
- Adverse Events
- GLP-1 and Endoscopy

# Timeline

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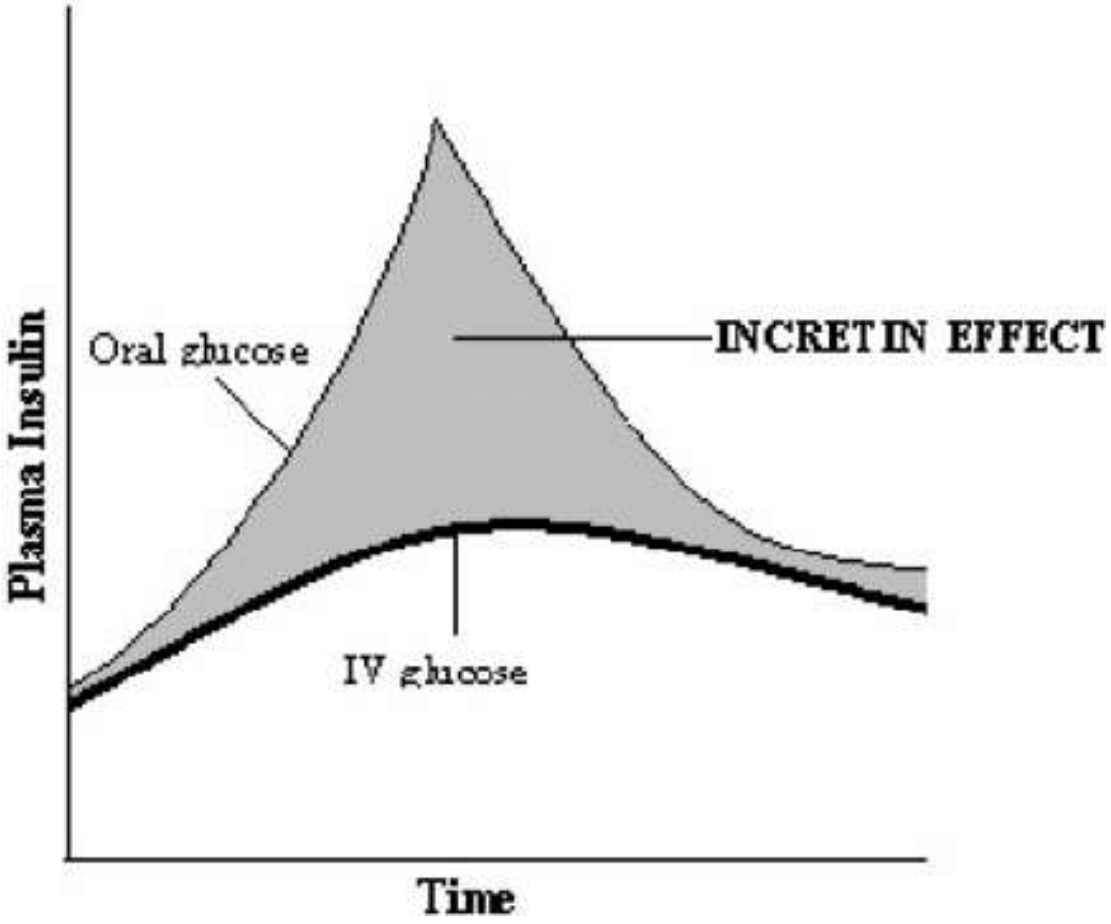
Gribble FM, et al. 2021 doi: 10.1038/s42255-020-00327-x.

# Discovery

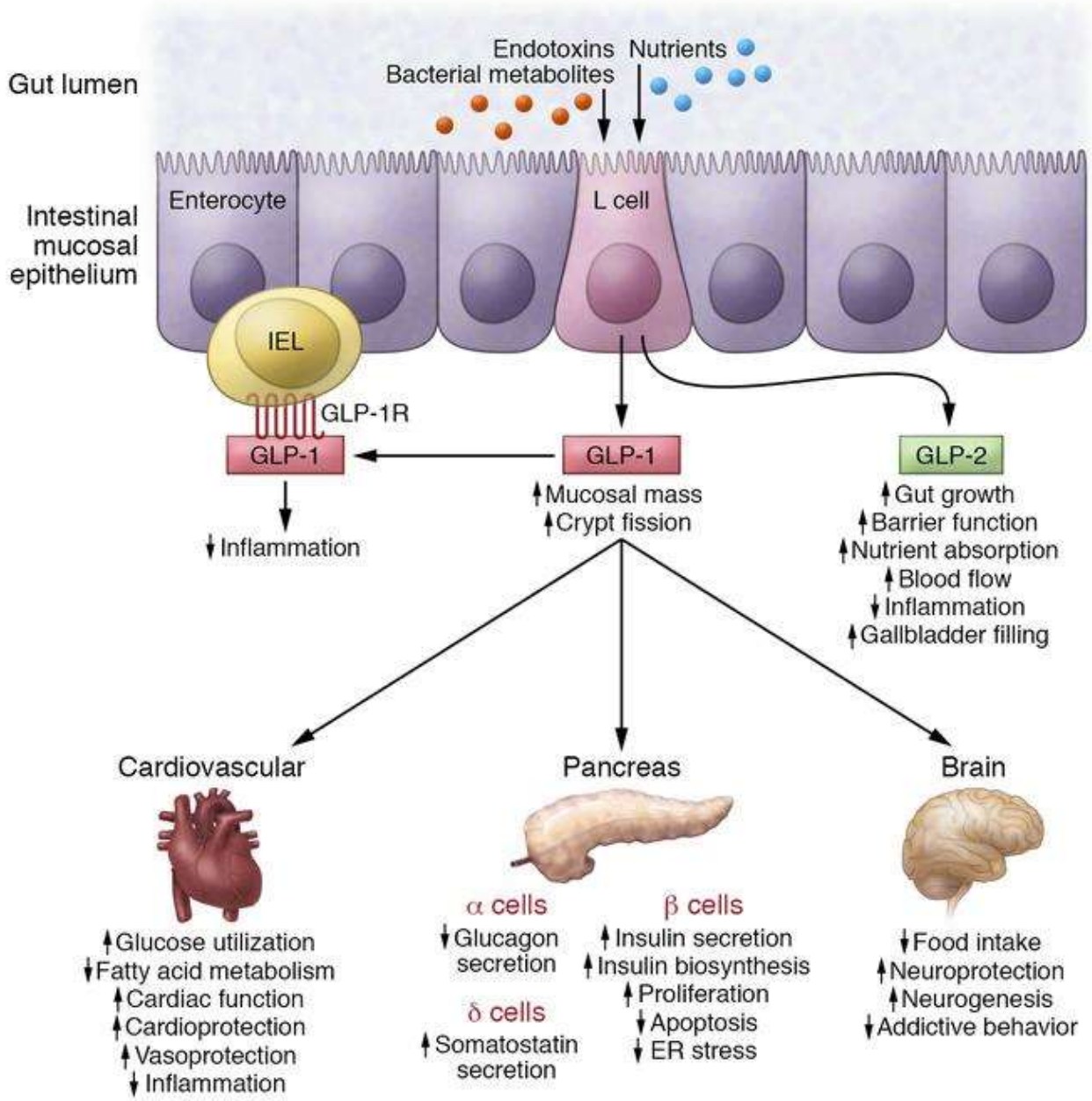



- Incretin effect
  - Hyperglycemia alone is not the sole stimulator of insulin
  - Humoral substance released from the jejunum during glucose consumption leading to increased insulin production



Chahal H, Chowdhury TA. QJM. 2007 Nov;100(11):671-7. PMID: 17881415.

# Mechanism of Action

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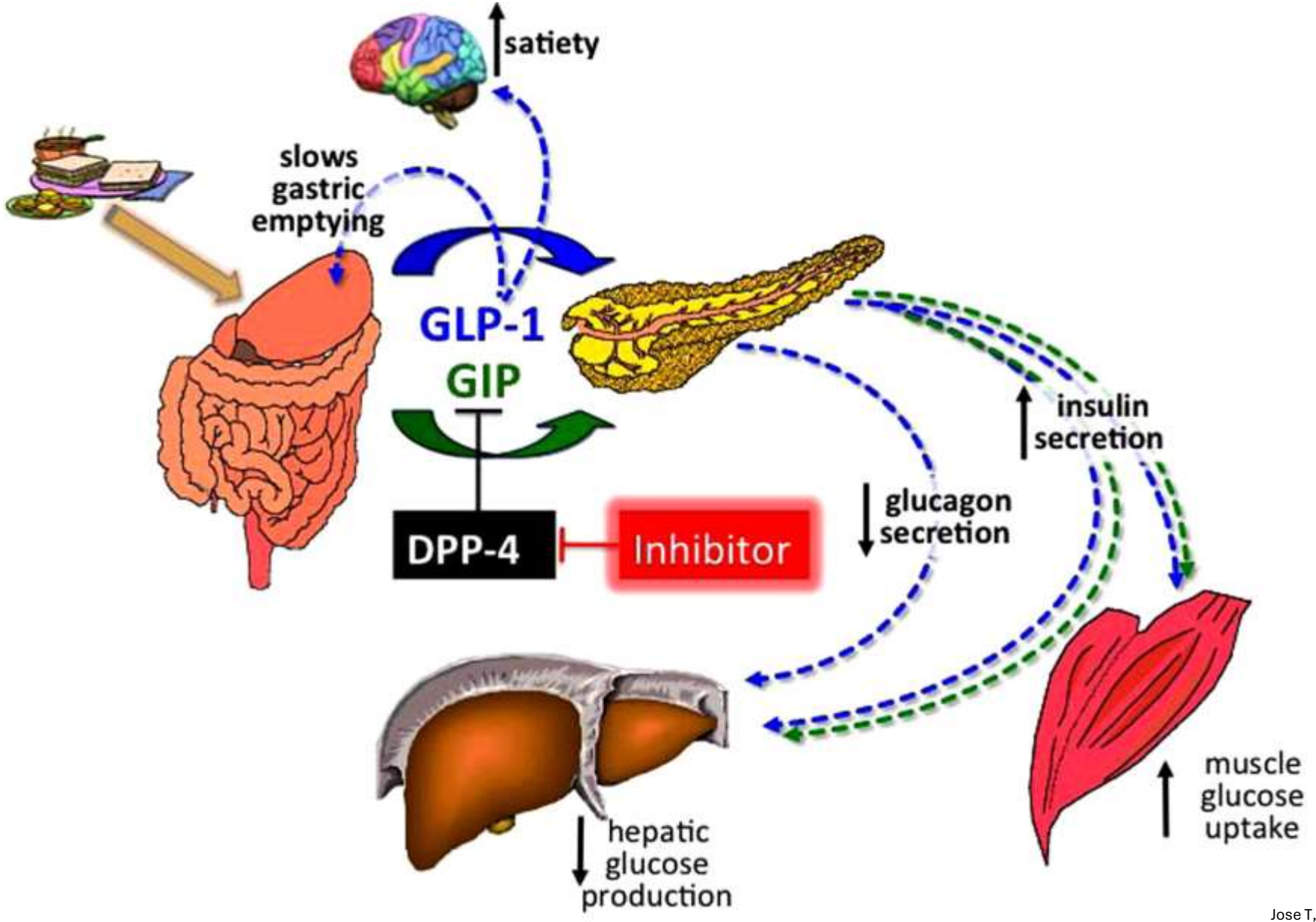
Drucker DJ, et al. J Clin Invest. 2017 Dec PMID: 29202475;

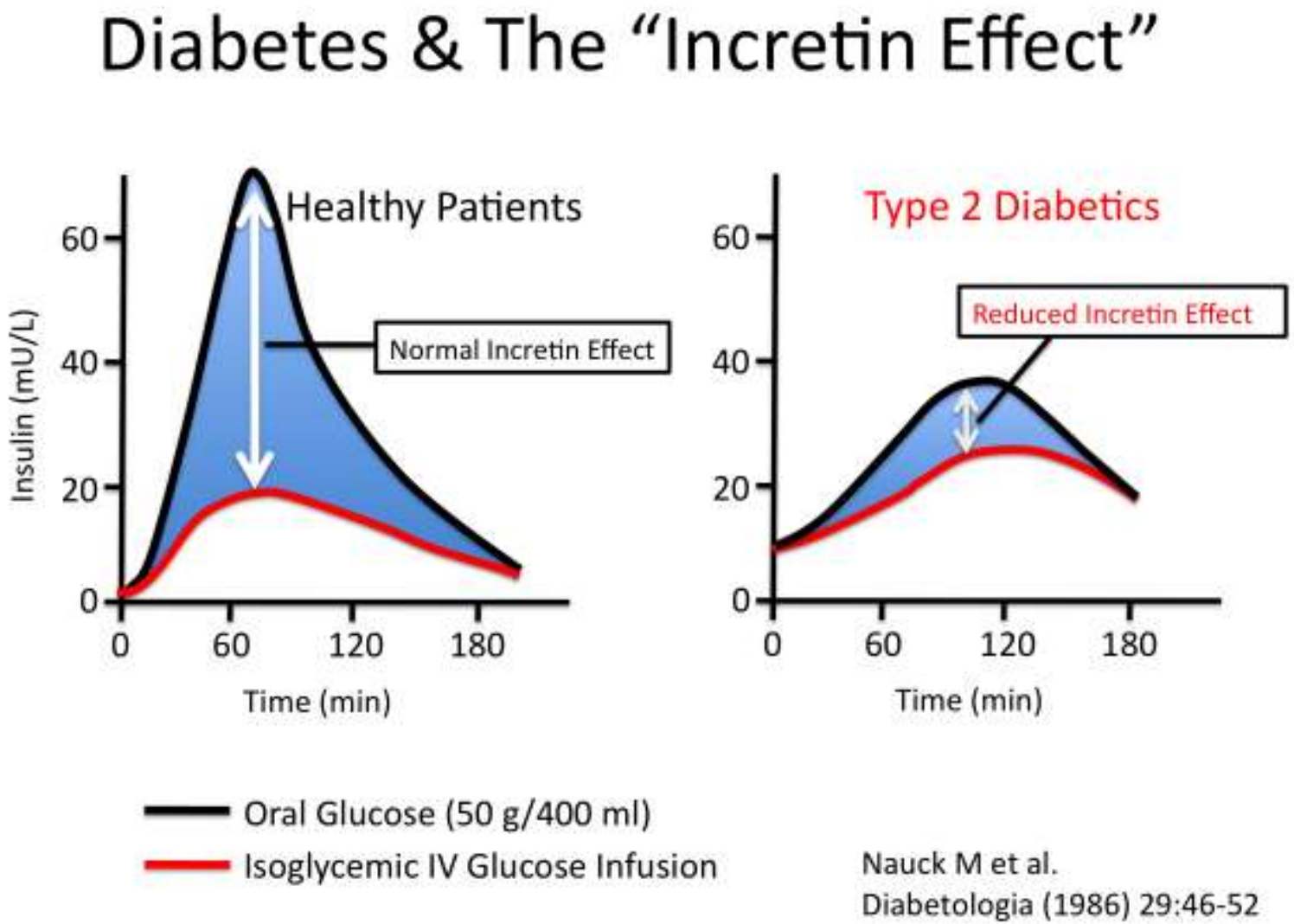
# Mechanism of Action






Jose T, et al. Diabetes and Vascular Disease Research. 2012 doi:10.1177/1479164111436236

# Type 2 Diabetes

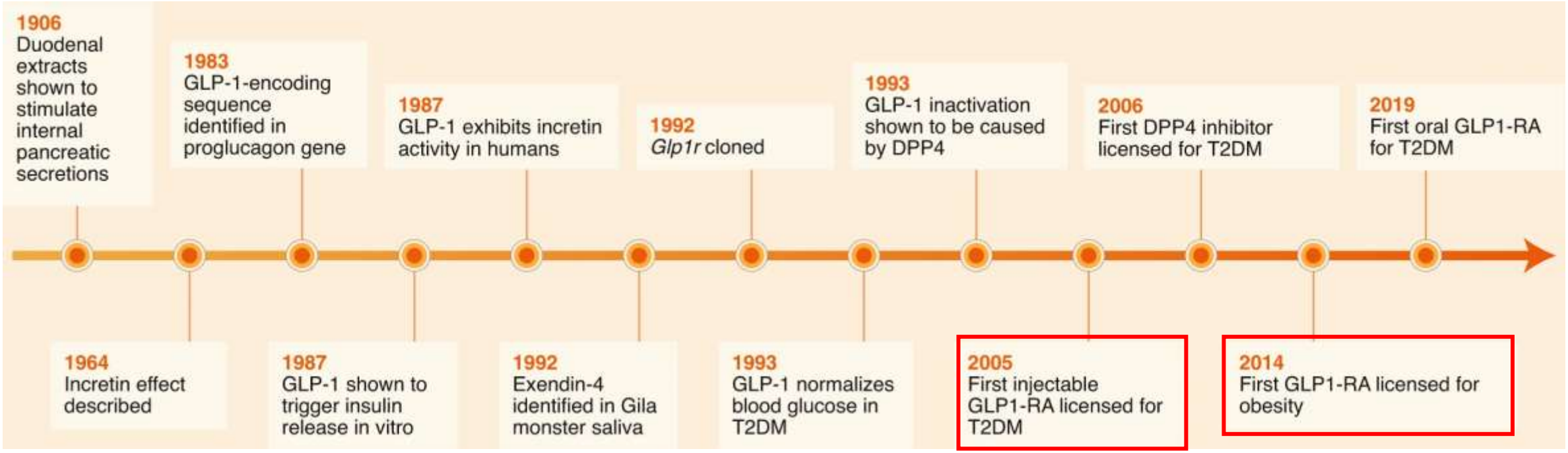



Nauck M et al.
Diabetologia (1986) 29:46-52

# Gila Monster

Exendin-4 in  its saliva which is resistant to DPP-4

# Timeline

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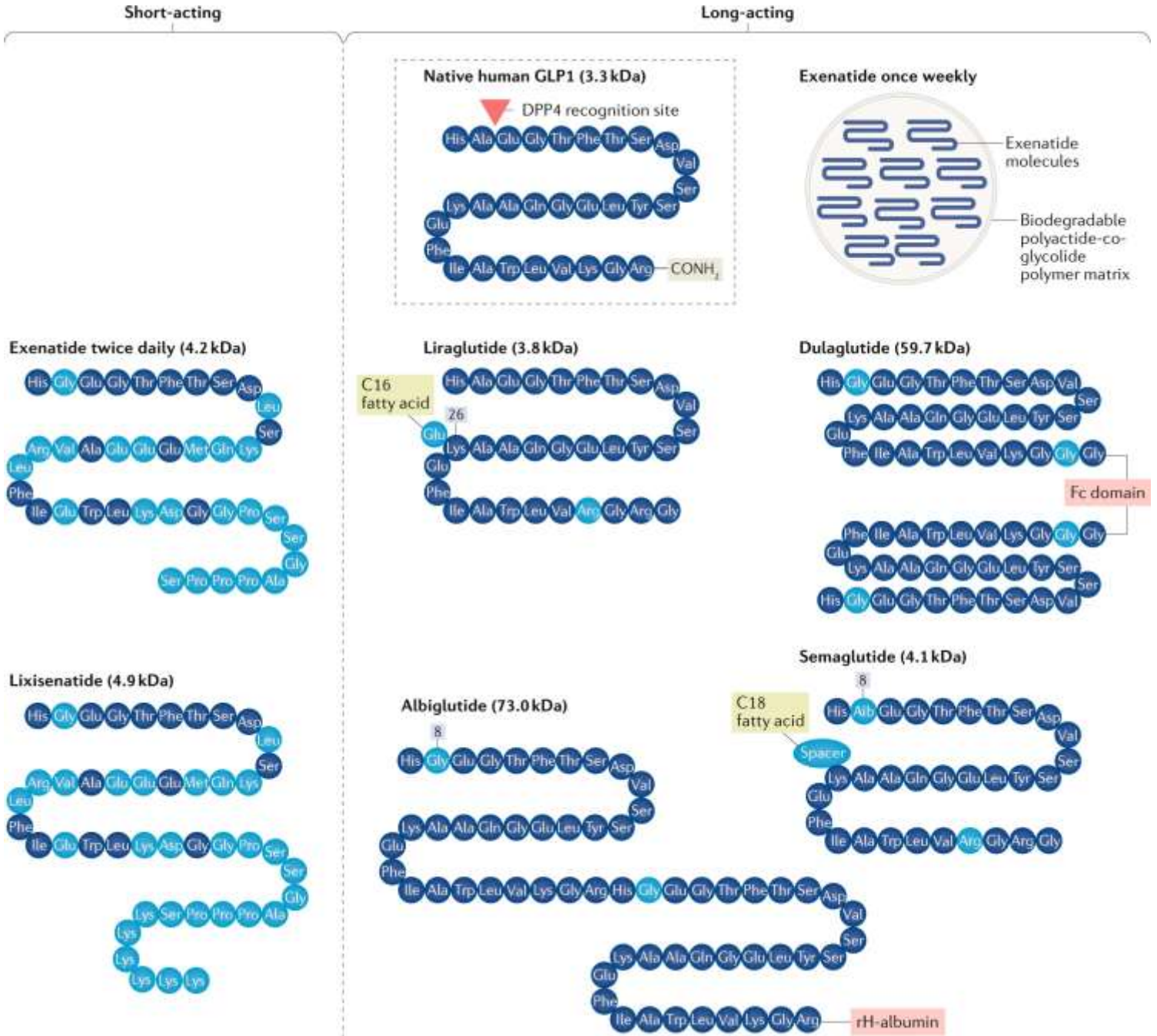
Gribble FM, et al. 2021 doi: 10.1038/s42255-020-00327-x.

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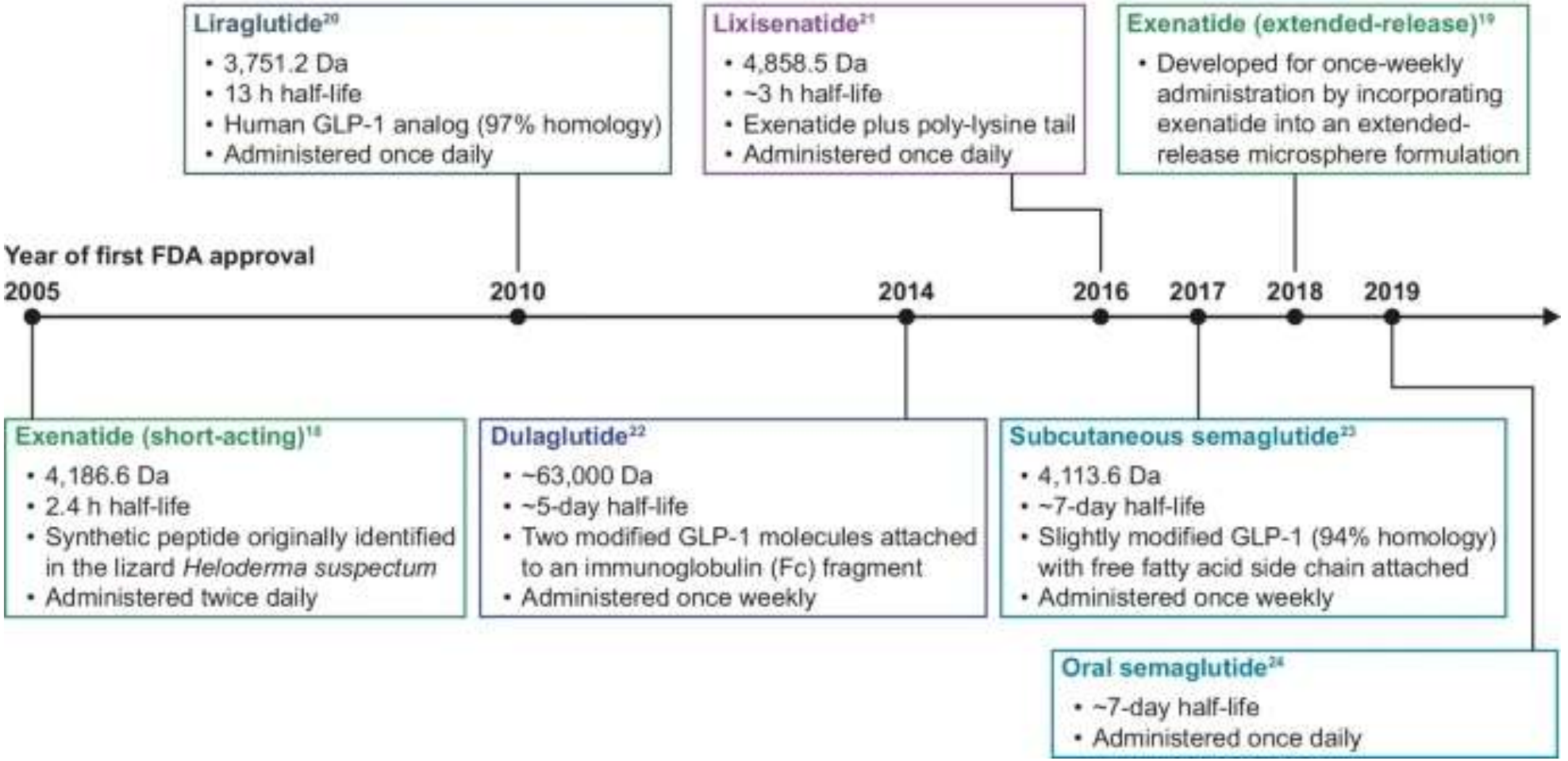
Andersen, A., *et al. Nat Rev Endocrinol* (2018). https://doi.org/10.1038/s41574-018-0016-2

# Timeline of Development

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Aroda VR, et al. Rev Endocr Metab Disord. 2022
doi: 10.1007/s11154-022-09735-8.

# Half Lives

- Native human GLP1 has half life of 1-2 minutes
- Synthetic GLP-1 has extended half lives
  - Exenatide (2005): 2.4 hours
    - Twice daily
  - Liraglutide (2010): 13 hours
    - Once daily
  - Dulaglutide (2014): ~5 days
  - Lixisenatide (2016): ~ 3 days
  - Semaglutide: (2017) ~ 7 days (165 hours)
  - Tirzepatide : (2022) ~ 5 days

# Landmark Trials

- Cardiovascular disease
- Type 2 diabetes
- Obesity
- MASLD/MASH

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

# Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

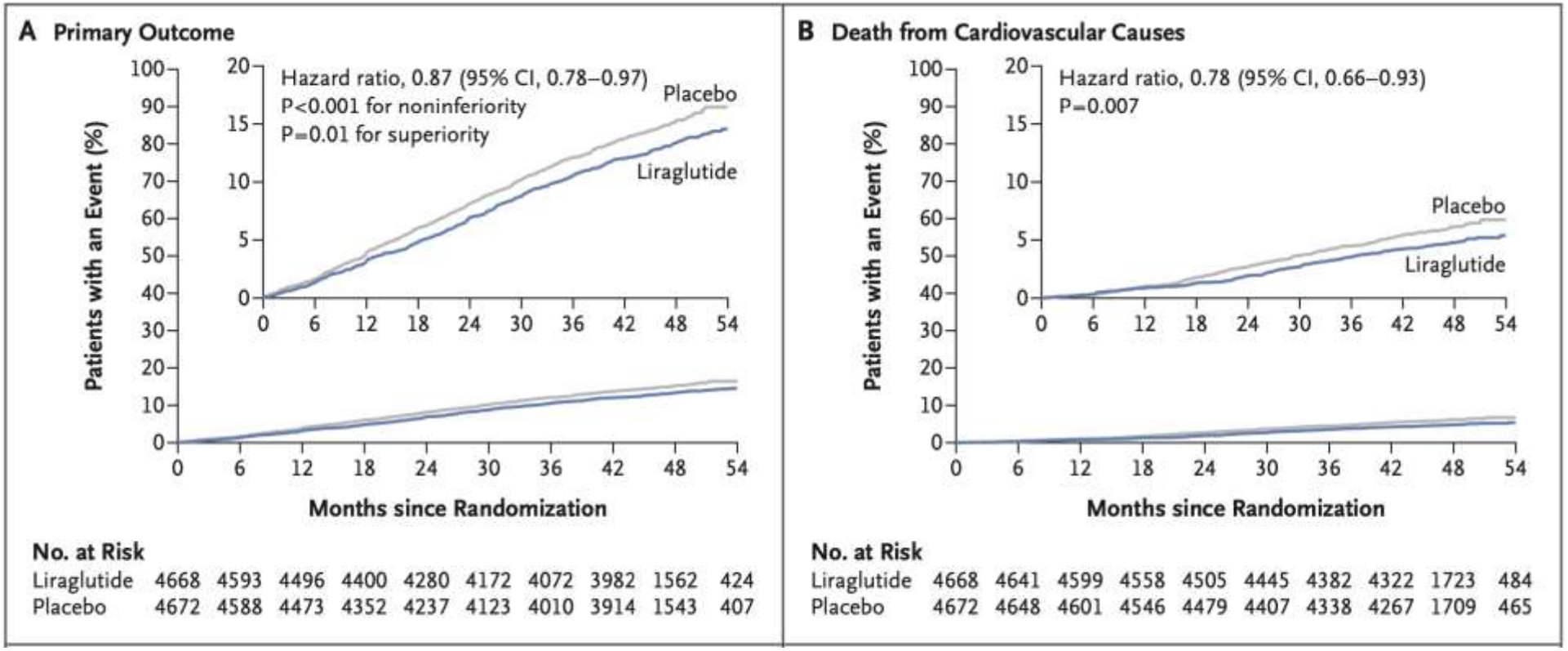
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette 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*

Double-blind placebo-controlled trial
Type 2 DM, A1c >7%
Age > 50 with known CV disease or CKD
Age >60 and CV risk factors

9340 patients
Median follow-up was 3.8 years

# Results

- Improvement of A1c 0.4%
- Weight loss - 2.3kg



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

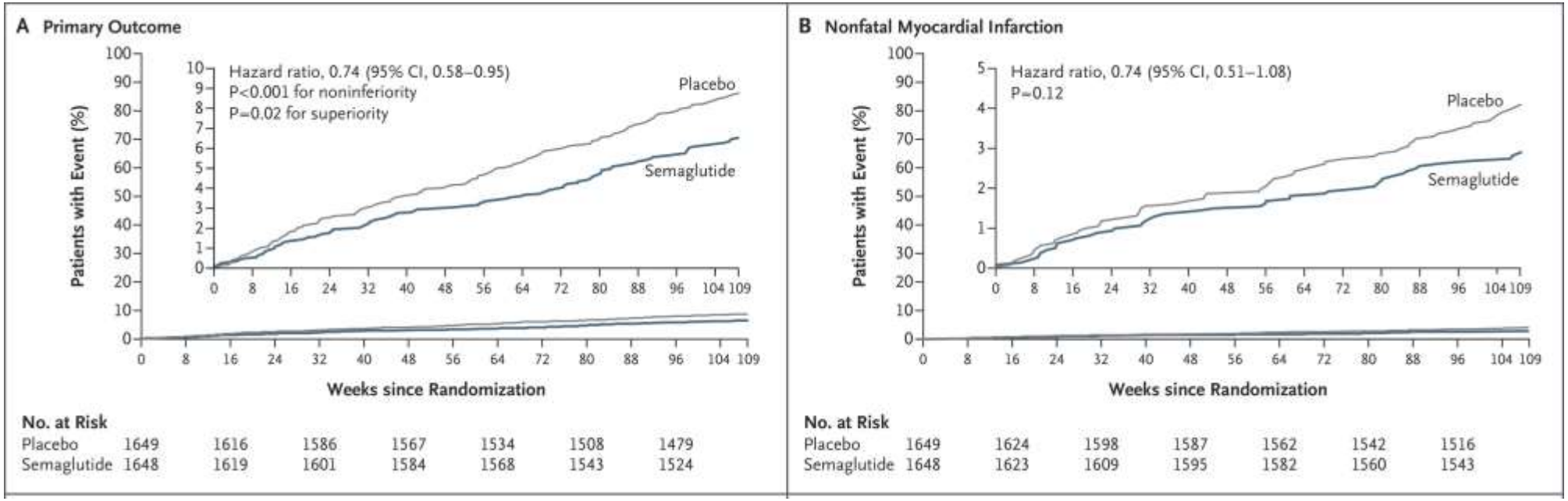
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

Randomized, double-blind, placebo-controlled
Type 2DM, A1c >7%
Age > 50 and known CV disease
Age > 60 and CV Risk Factors

3297 patients
Median follow up 2.1 years

# Results

- Improvement of A1c -1.4%
- Weight loss – 4.9kg

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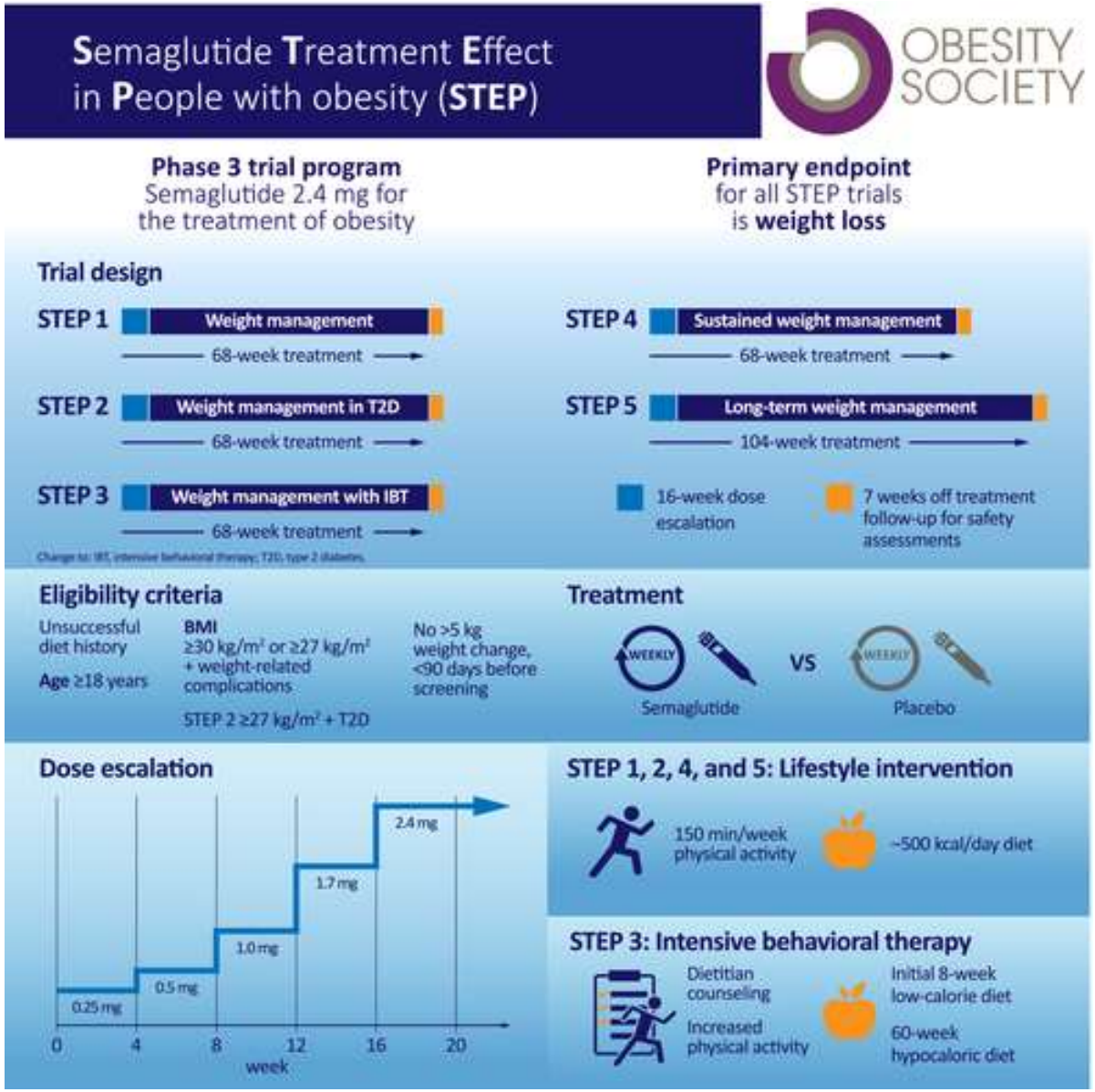
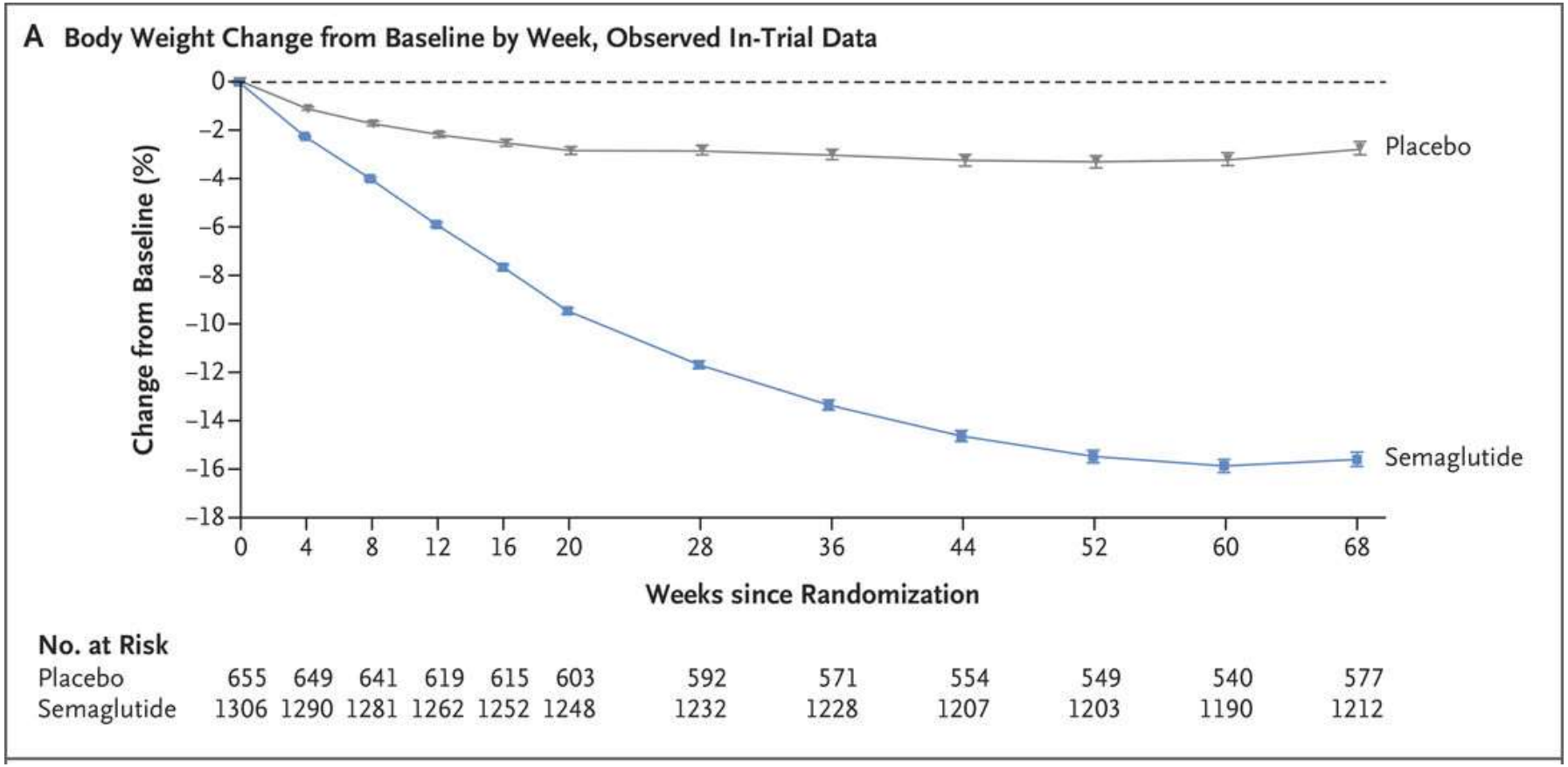
# Semaglutide and obesity



# Semaglutide and obesity




Mean weight change at week 68 was −14.9% with 2.4-mg semaglutide, as compared with −2.4% with placebo

Kushner RF, et al. Obesity (Silver Spring). 2020 doi: 10.1002/oby.22794.

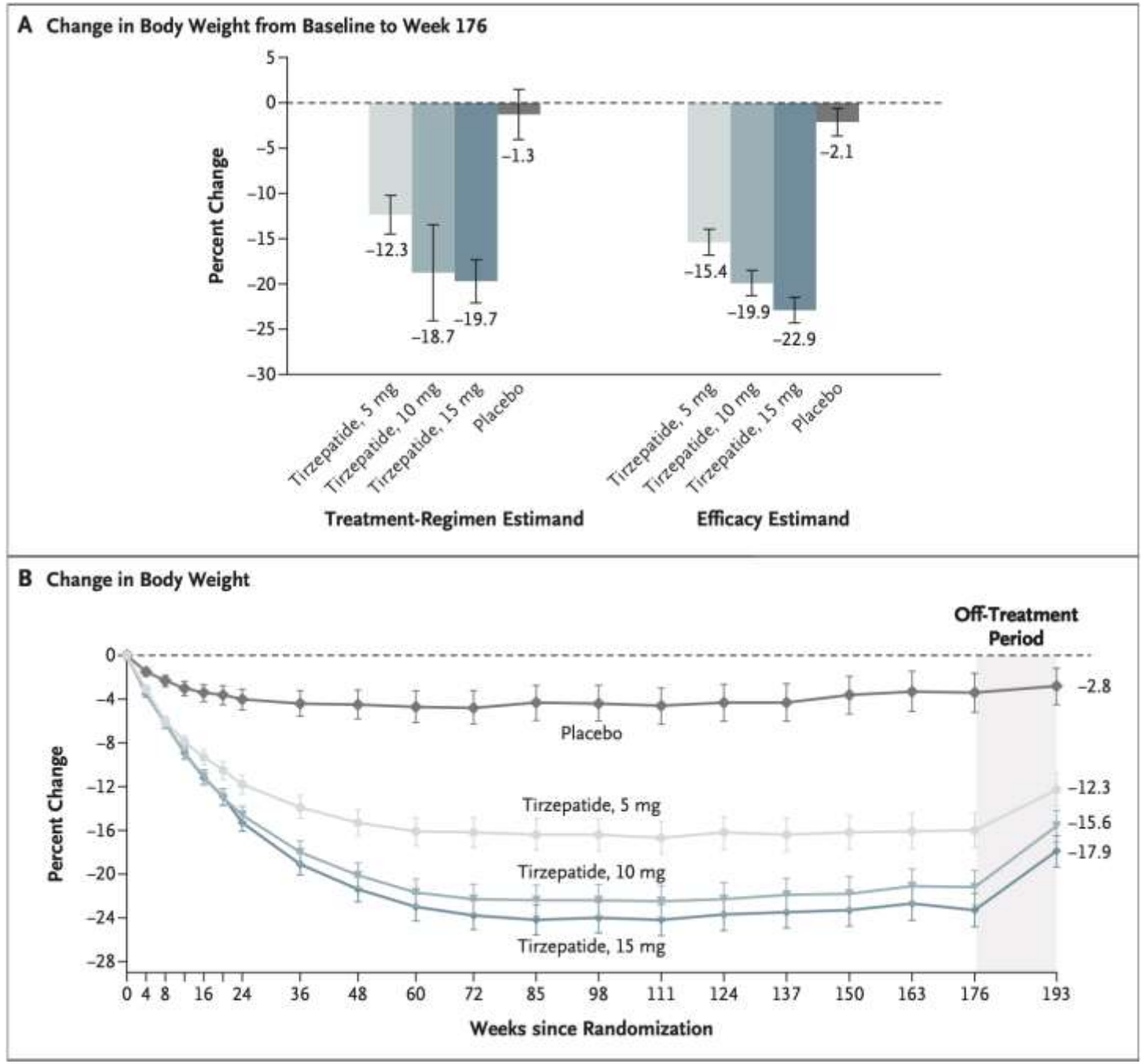
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

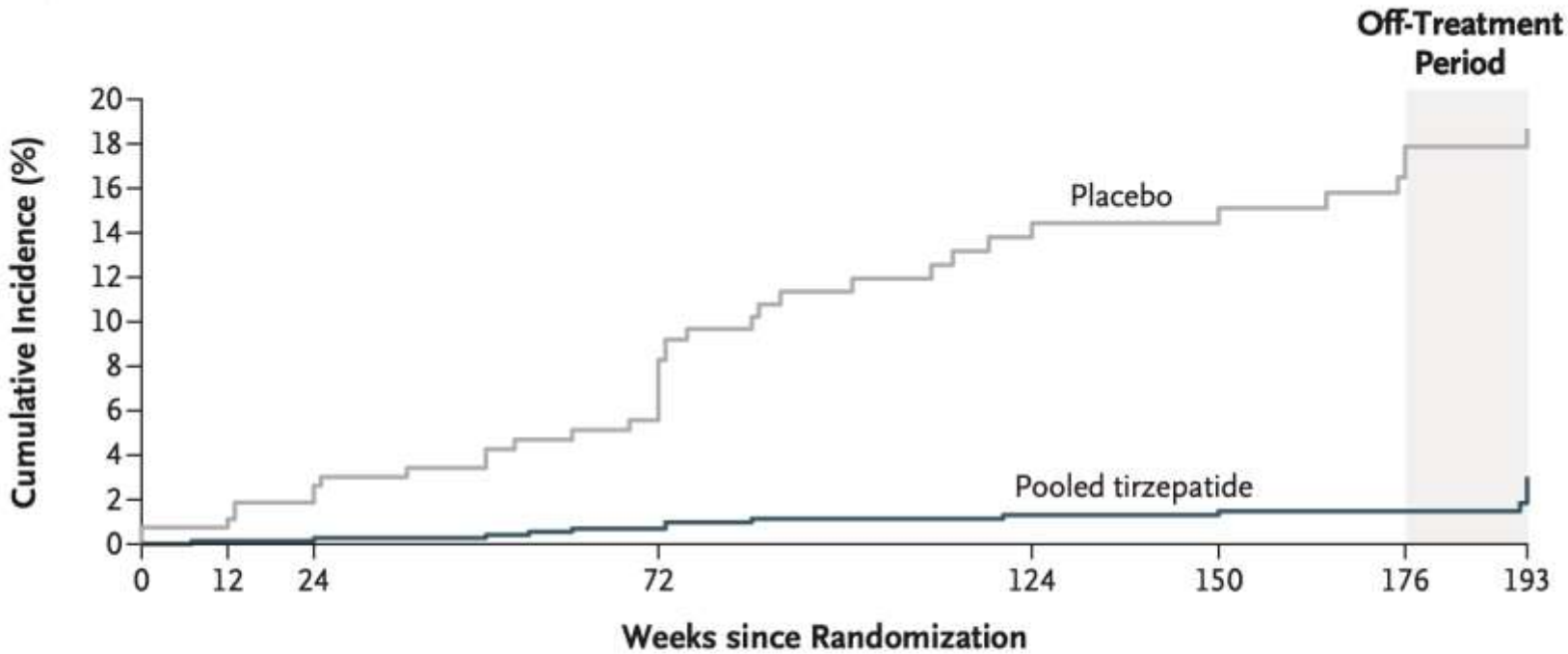
# Tirzepatide for Obesity Treatment and Diabetes Prevention

Ania M. Jastreboff, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Adam Stefanski, M.D., Ph.D., Louis J. Aronne, M.D., Bruno Halpern, M.D., Ph.D., Sean Wharton, M.D., Pharm.D., John P.H. Wilding, D.M., Leigh Perreault, M.D., Shuyu Zhang, M.S., Ramakrishna Battula, M.S., Mathijs C. Bunck, M.D., Ph.D., Nadia N. Ahmad, M.D., M.P.H., and Irina Jouravskaya, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Double-blind, randomized, controlled trial
2539 participants with obesity


A Change in Body Weight from Baseline to Week 176
Percent Change
5
0
−5
−10
−15
−20
−25
−30
−12.3
−18.7
−19.7
−1.3
−15.4
−19.9
−22.9
−2.1
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Placebo
Treatment-Regimen Estimand
Efficacy Estimand
B Change in Body Weight
Off-Treatment Period
Percent Change
0
−4
−8
−12
−16
−20
−24
−28
Placebo
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
−2.8
−12.3
−15.6
−17.9
0 4 8 16 24 36 48 60 72 85 98 111 124 137 150 163 176 193
Weeks since Randomization

**C** Incidence of Type 2 Diabetes




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **No. at Risk** | | | | | | | | |
| Placebo | 270 | 266 | 257 | 209 | 137 | 126 | 121 | 99 |
| Pooled tirzepatide | 762 | 751 | 742 | 700 | 581 | 570 | 557 | 494 |
| **No. of Participants with Diagnosis** | | | | | | | | |
| Placebo | 2 | 3 | 7 | 20 | 31 | 32 | 36 | 37 |
| Pooled tirzepatide | 0 | 1 | 2 | 5 | 9 | 10 | 10 | 18 |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

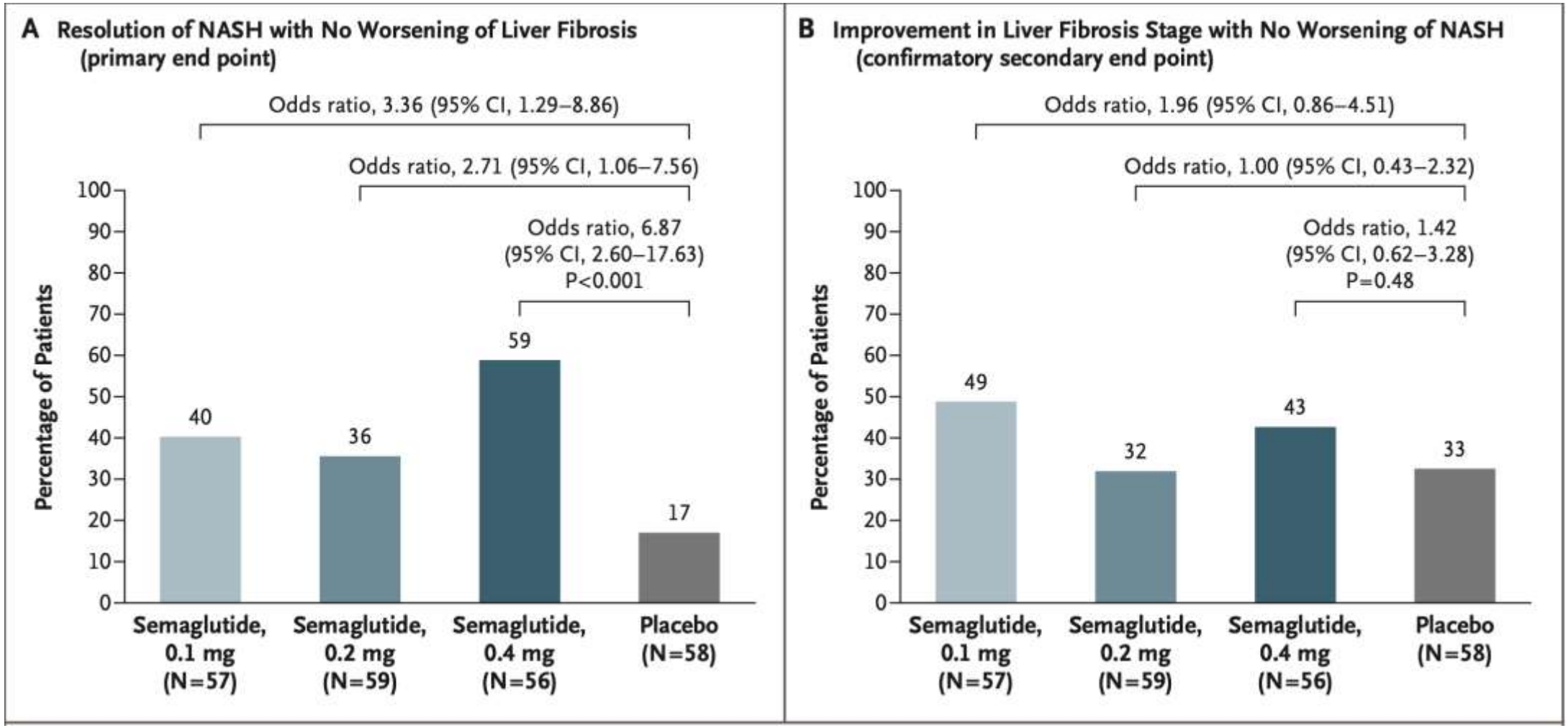
# A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

72-week, double-blind phase 2 trial involving patients with biopsy- confirmed NASH and liver fibrosis of stage F1, F2, or F3

Once-daily subcutaneous semaglutide at a dose of 0.1, 0.2, or 0.4 mg or corresponding placebo

320 patients


A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)
Odds ratio, 3.36 (95% CI, 1.29–8.86)
Odds ratio, 2.71 (95% CI, 1.06–7.56)
Odds ratio, 6.87 (95% CI, 2.60–17.63) P<0.001
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
40
36
59
17
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)
B Improvement in Liver Fibrosis Stage with No Worsening of NASH (confirmatory secondary end point)
Odds ratio, 1.96 (95% CI, 0.86–4.51)
Odds ratio, 1.00 (95% CI, 0.43–2.32)
Odds ratio, 1.42 (95% CI, 0.62–3.28) P=0.48
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
49
32
43
33
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)

# Semaglutide and Adverse Events

| Adverse events | Continued semaglutide, 2.4 mg/wk (n = 535) | | | Switched to placebo (n = 268) | | |
|---|---|---|---|---|---|---|
| | No. (%) of participants | No. of events | Events per 100 patient-years[a] | No. (%) of participants | No. of events | Events per 100 patient-years[a] |
| Any adverse event | 435 (81.3) | 1885 | 346.3 | 201 (75.0) | 779 | 292.8 |
| Serious adverse events | 41 (7.7) | 51 | 9.4 | 15 (5.6) | 19 | 7.1 |
| Discontinuation of trial product due to adverse events[b] | 13 (2.4) | | | 6 (2.2) | | |
| Fatal events[c,d] | 1 (0.2) | 1 | 0.2 | 1 (0.4) | 2 | 0.7 |
| Adverse events reported in ≥5% of participants[e] | | | | | | |
| Diarrhea | 77 (14.4) | 114 | 20.9 | 19 (7.1) | 26 | 9.8 |
| Nausea | 75 (14.0) | 105 | 19.3 | 13 (4.9) | 13 | 4.9 |
| Constipation | 62 (11.6) | 75 | 13.8 | 17 (6.3) | 19 | 7.1 |
| Nasopharyngitis | 58 (10.8) | 77 | 14.1 | 39 (14.6) | 54 | 20.3 |
| Vomiting | 55 (10.3) | 88 | 16.2 | 8 (3.0) | 13 | 4.9 |
| Headache | 41 (7.7) | 48 | 8.8 | 10 (3.7) | 10 | 3.8 |
| Influenza | 39 (7.3) | 45 | 8.3 | 19 (7.1) | 23 | 8.6 |
| Abdominal pain | 35 (6.5) | 46 | 8.5 | 8 (3.0) | 10 | 3.8 |
| Back pain | 28 (5.2) | 32 | 5.9 | 18 (6.7) | 19 | 7.1 |
| Arthralgia | 25 (4.7) | 28 | 5.1 | 14 (5.2) | 16 | 6.0 |

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Rubino D, et al.. *JAMA*. 2021
doi:10.1001/jama.2021.322

# GLP-1 Agonists and Adverse Events

| Outcomes | GLP-1 agonists, HR (95% CI)[a] Crude | Adjusted[b] | Bupropion-naltrexone |
|---|---|---|---|
| **Primary analysis** | | | |
| Biliary disease | 1.48 (0.88-2.47) | 1.50 (0.89-2.53) | 1 [Reference] |
| Pancreatitis | 10.33 (1.44-74.40) | 9.09 (1.25-66.00) | 1 [Reference] |
| Bowel obstruction | 5.16 (1.27-21.00) | 4.22 (1.02-17.40) | 1 [Reference] |
| Gastroparesis | 3.31 (1.04-10.50) | 3.67 (1.15-11.90) | 1 [Reference] |
| **Sensitivity analyses** | | | |
| Exclusion of hyperlipidemia | | | |
| Biliary disease | 1.50 (0.88-2.56) | 1.46 (0.84-2.51) | 1 [Reference] |
| Pancreatitis | 9.80 (1.36-70.79) | 7.99 (1.10-58.30) | 1 [Reference] |
| Bowel obstruction | 4.43 (1.08-18.20) | 3.63 (0.87-15.10) | 1 [Reference] |
| Gastroparesis | 3.32 (1.04-10.60) | 3.67 (1.14-11.80) | 1 [Reference] |
| Analysis with less-restrictive obesity definition[c] | | | |
| Biliary disease | 1.29 (0.92-1.80) | 1.20 (0.85-1.69) | 1 [Reference] |
| Pancreatitis | 6.19 (1.99-19.30) | 5.94 (1.90-18.60) | 1 [Reference] |
| Bowel obstruction | 3.11 (1.28-7.54) | 2.44 (1.00-5.95) | 1 [Reference] |
| Gastroparesis | 2.11 (1.09-4.09) | 2.35 (1.20-4.58) | 1 [Reference] |
| E-values for adjusted HRs[d] | | | |
| Biliary disease | 2.36 | | |
| Pancreatitis | 17.67 | | |
| Bowel obstruction | 7.91 | | |
| Gastroparesis | 6.80 | | |

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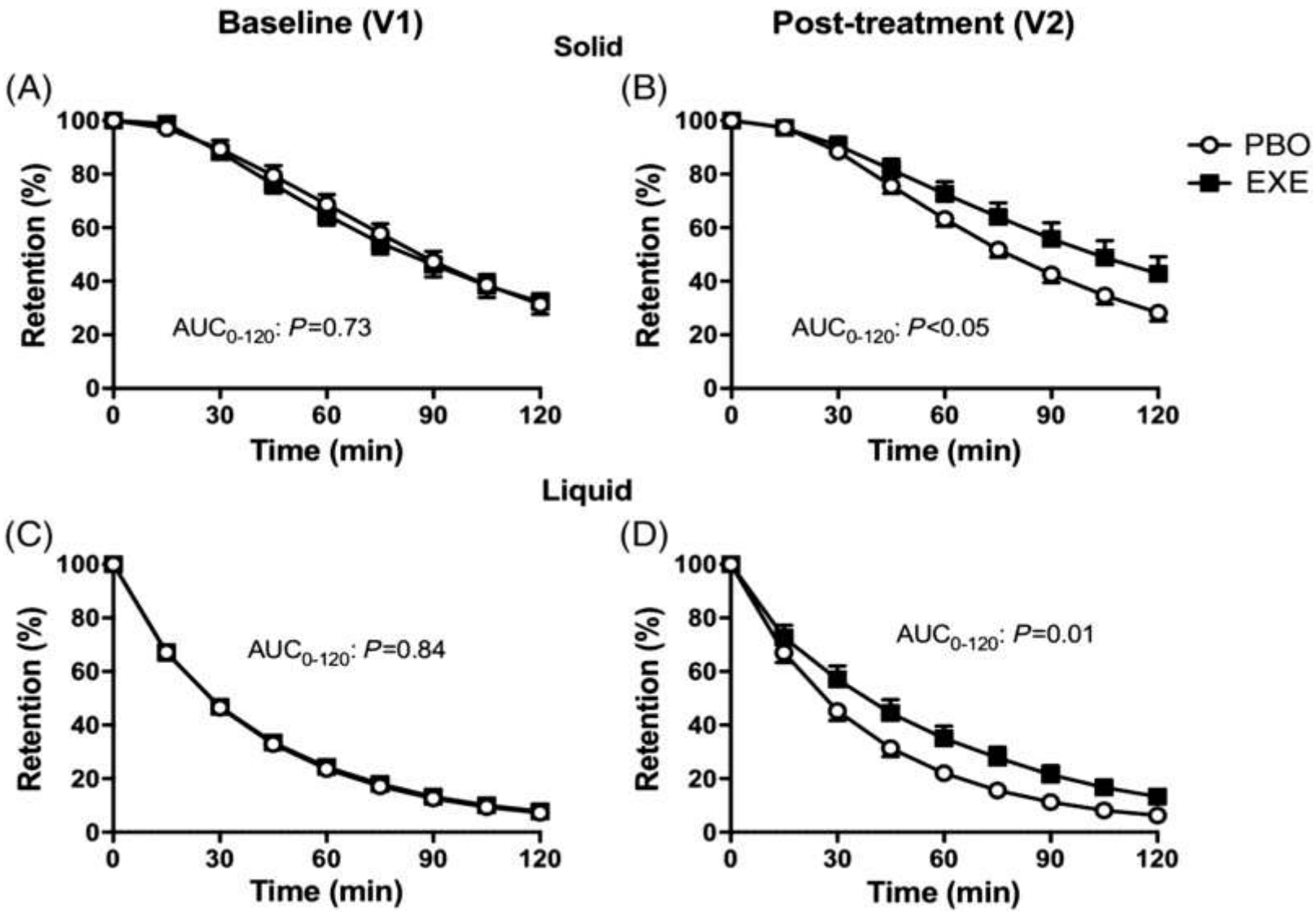
Sodhi M, et al *JAMA*. doi:10.1001/jama.2023.19574

# How to manage side effects

- Educate patients on side effects
- Titrate dose appropriately
  - Consider downtitrating or titrating more slowly
  - Individual approach on dosing
- Treat symptoms
- Always consider history of pancreatitis, gastroparesis prior to initiating

# Exenatide and Gastric Emptying

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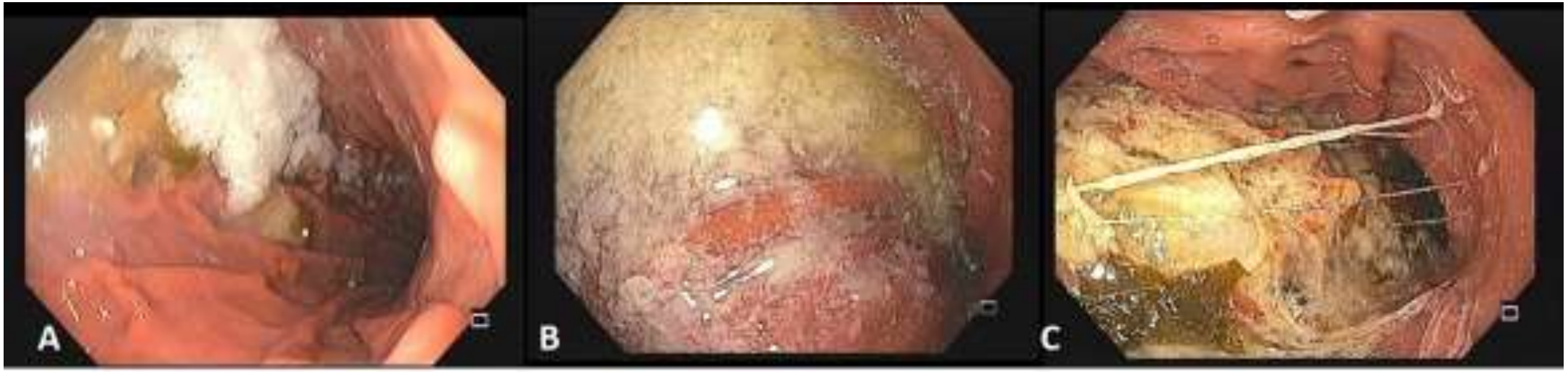
Jones KL et al. Diabetes Obes Metab. 2020
doi: 10.1111/dom.13956.

# GLP-1 and Endoscopy

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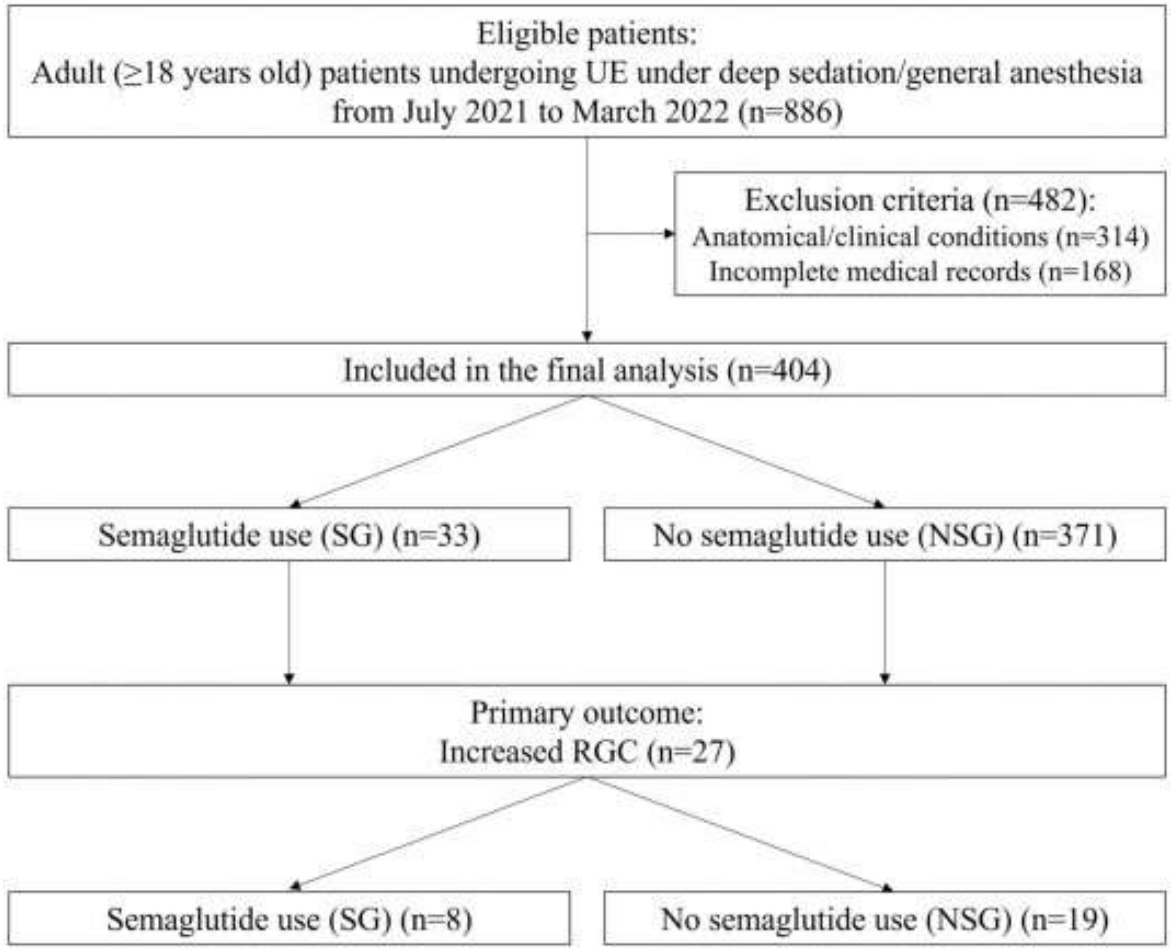
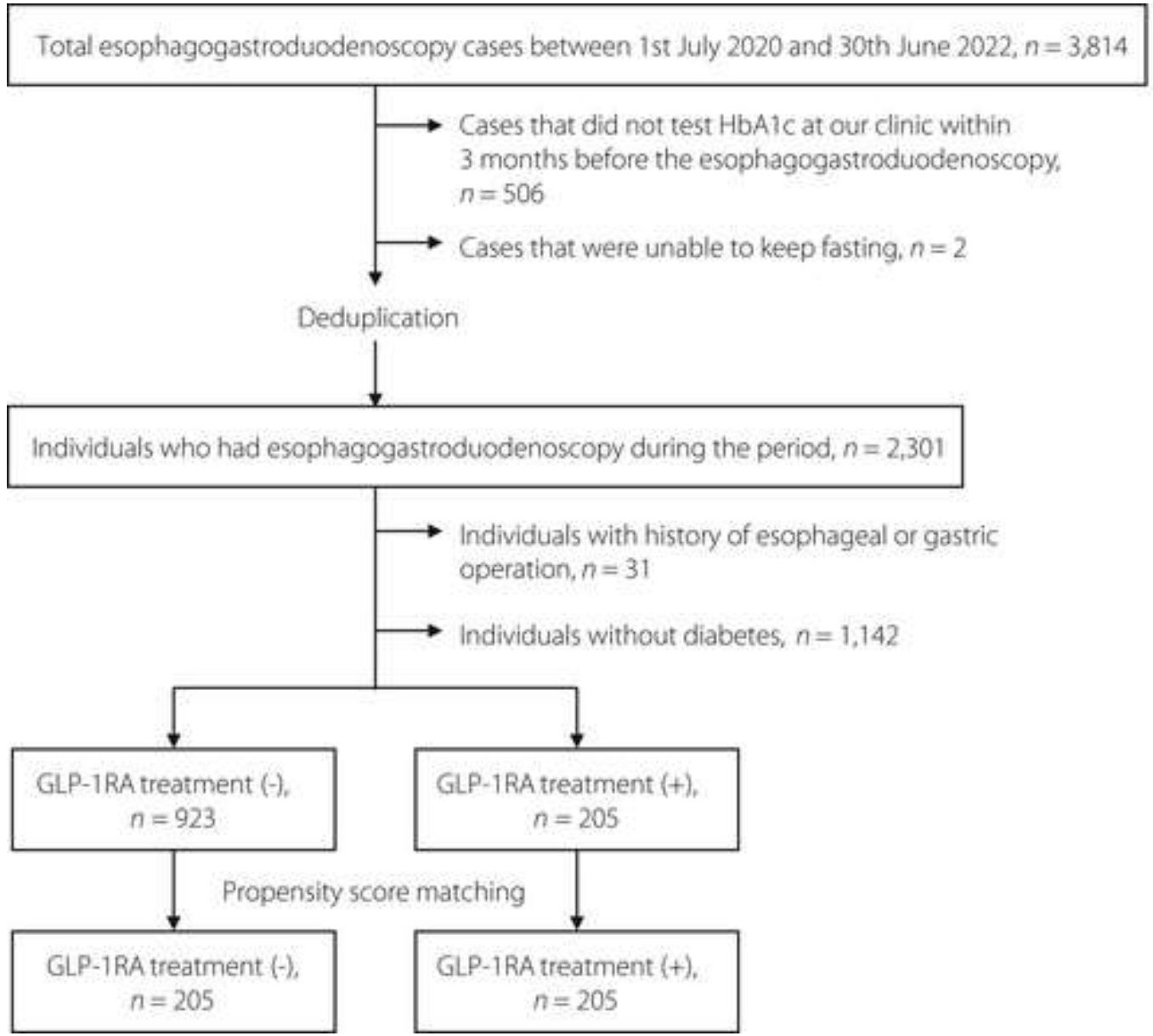
Silveira SQ et al. J Clin Anesth. 2023
doi: 10.1016/j.jclinane.2023.111091.




24.2% 5.1% $p < 0.001$

When EGD was was combined with colonoscopy a protective [PR = 0.13 (95%CI 0.15–0.78)] effect against increased RGC was observed.

Silveira SQ et al. J Clin Anesth. 2023
doi: 10.1016/j.jclinane.2023.111091.

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Kobori T, et al. J Diabetes Investig. 2023 doi: 10.1111/jdi.14005.

# GLP 1 Agonists and Endoscopy

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | GLP-1RA (–) (*n* = 923) | GLP-1RA (+) (*n* = 205) | *P*-value | GLP-1RA (–) (*n* = 205) | GLP-1RA (+) (*n* = 205) | *P*-value |
| Gastric residue (+) | 6 (0.65) | 11 (5.4) | <0.001 | 1 (0.49) | 11 (5.4) | 0.004 |

GLP-1RA prescribed for the 11 patients with gastric residue were liraglutide once daily 1.8 mg (n = 2), dulaglutide once weekly 0.75 mg (n = 5), semaglutide once weekly 0.5 mg (n = 2) and semaglutide once weekly 1.0 mg (n = 2).

# American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

- For patients on daily dosing consider holding GLP-1 agonists on the day of the procedure/surgery.
- For patients on weekly dosing consider holding GLP-1 agonists a week prior to the procedure/surgery.
- If the patient has no GI symptoms, but the GLP-1 agonists were not held as advised, proceed with ‘full stomach’ precautions or consider evaluating gastric volume by ultrasound, if possible and if proficient with the technique.



https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

Clinical Gastroenterology and Hepatology 2024;22:705–707

# CLINICAL PRACTICE UPDATES

## AGA Rapid Clinical Practice Update on the Management of Patients Taking GLP-1 Receptor Agonists Prior to Endoscopy: Communication



- The ASA used such terms as “suggest,” “consider,” and “advise,” as we would in an AGA Clinical Practice Update.
  - Were a rigorous guideline produced using GRADE methodology, there would be insufficient evidence to support recommendations derived from corresponding PICOs.
- We suggest that an individualized approach be taken to managing patients on GLP-1 RAs in the pre-endoscopic setting.
  - The clinical team should be cognizant of the indication for the GLP-1 RAs, because cessation in patients relying on this medication for diabetes management might provide more risk than benefit.
- Adding more complexity to periprocedural medication management, this may necessitate enhanced nursing resources (which are scarce), and exacerbate barriers and care delays for patients requiring endoscopic procedures.

Clinical Gastroenterology and Hepatology 2024;22:705–707

# CLINICAL PRACTICE UPDATES

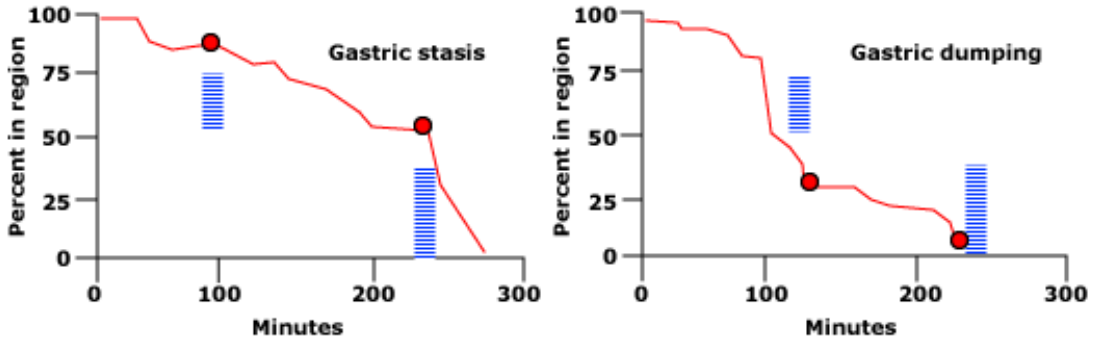
## AGA Rapid Clinical Practice Update on the Management of Patients Taking GLP-1 Receptor Agonists Prior to Endoscopy: Communication

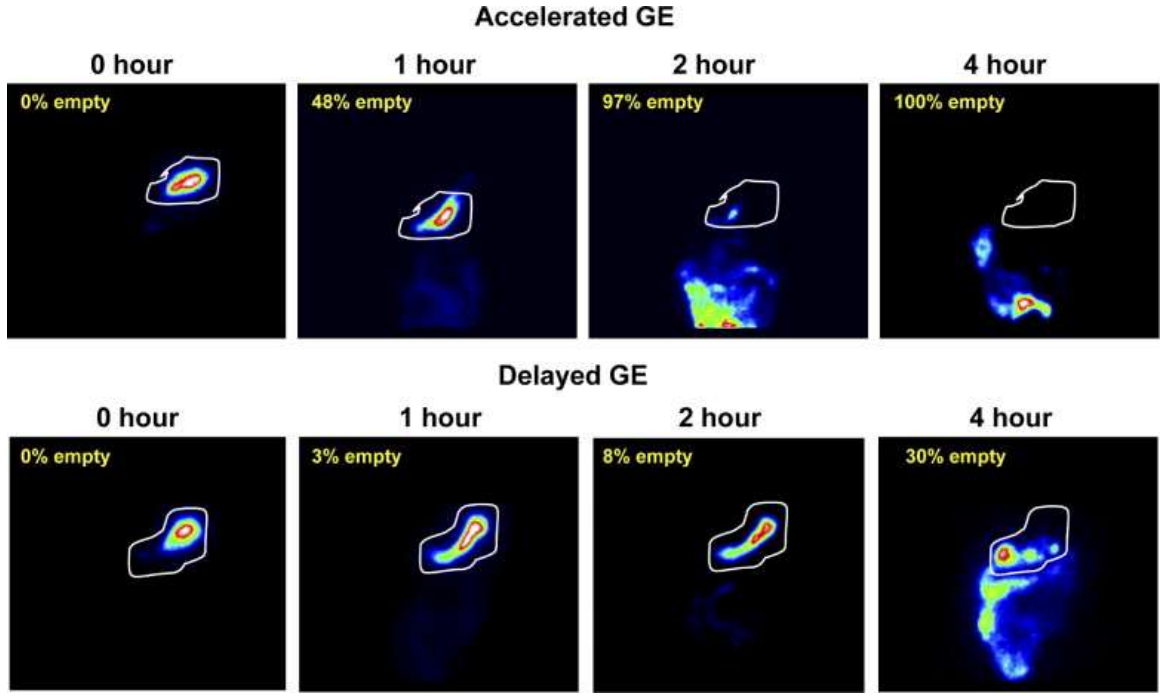


- in patients on GLP-1 RAs who have followed standard perioperative procedures (typically an 8-hour solid-food fast and a 2-hour liquid fast) and who do not have symptoms of nausea, vomiting, dyspepsia, or abdominal distention, we advise proceeding with upper and/or lower endoscopy.
- In patients with symptoms suggesting possible retained gastric contents, transabdominal ultrasonography can be used to assess the stomach (if there is sufficient clinical expertise and the equipment is available) but evidence to support this modality in standard practice is lacking.
- In symptomatic patients for whom delaying endoscopy may have negative clinical consequences, rapid-sequence intubation is a consideration; however, this may not be possible in most ambulatory or office-based endoscopy settings.
- When possible, placing patients on a liquid diet the day before sedated procedures may be a more acceptable strategy, in lieu of stopping GLP-1 RAs, and more consistent with the holistic preprocedural management of other similar conditions.

# Gastric emptying testing

- 4 hour Gastric scintigraphy = gold standard
- (Tc)-99m labeled low fat egg-white, 2 slices bread and jam with water
- Imaging performed at 0, 1, 2, and 4 hours
  - Delay = retention >90% at 1 hr, >60% 2 hr, >10% at 4 hours
- 4hr test may increase diagnostic yield by 25% vs. 2hr



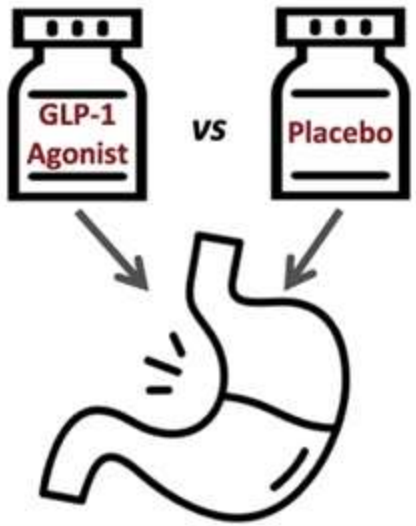





Abell TL et al, consensus recommendations, J Nucl Med Technol 2008
Guo JP et al, DDS 2001: 46 (1)

# Quantified Metrics of Gastric Emptying Delay by GLP-1 Agonists: A Systematic Review and Meta-Analysis

Systematic Review: n=36
Meta-Analysis: n=15




## Quantified Gastric Emptying Delay: GLP-1 Agonists Relative to Placebo

**Solids**

Gastric Emptying Scintigraphy

N=247

**36 minutes delay on $T_{1/2}$**

**Liquids**

Acetaminophen Absorption Test

N=284

**No delay on $T_{max}$**

## Perioperative Care of Patients on GLP-1 Agonist

- ☑ **Continue GLP-1 Agonist**
- ☑ **Liquid diet on day prior to procedure**
- ☑ **Standard pre-anesthesia fasting period**

Hiramoto et al. *Am J Gastroenterol.* 2024. doi:10.14309/ajg.0000000000002820

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