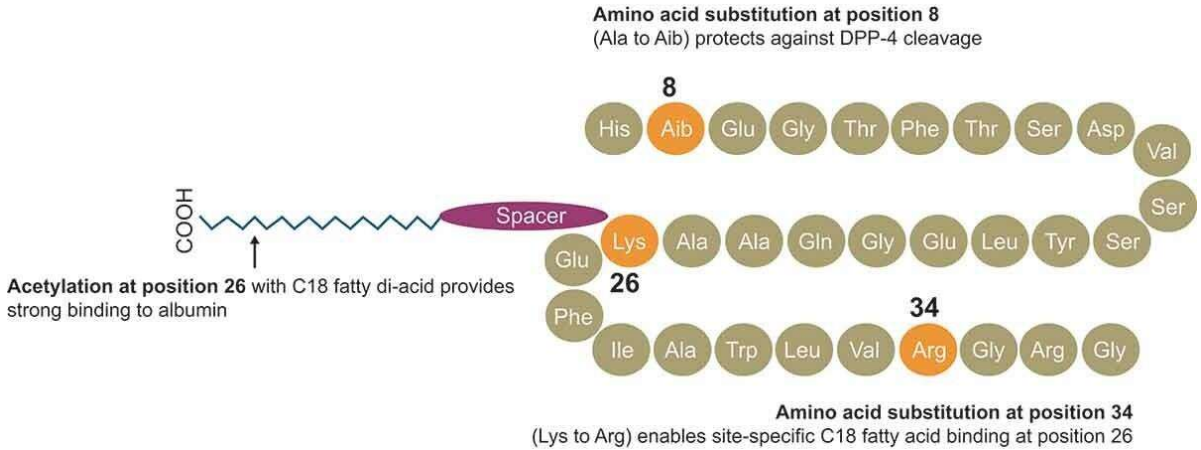
Semaglutide



- Semaglutide - human GLP-1 analog with
- 94% amino acid homology to native GLP-1
- half-life of approximately 1 week
- Three important structural modifications - to the semaglutide molecule that extend its half-life to approximately 1 week

Semaglutide – available evidence

STEP trials – primary **obesity** (2.4mg weekly)

- STEP-Teens (12-18 years)
- STEP 1 to 5 trials

SUSTAIN trials (1-7) – primarily **diabetes** (0.5 and 1.0mg weekly)

- 2,3,4 – combination with other DM medications
- Sustain 7- Sema vs. Dulagutide
- Sustain 6 Sema vs Liraglutide

SELECT CVOT trial

OASIS & PIONEER - oral semaglutide

- **PIONEER 6: CVOT of Oral semaglutide**
  - Semaglutide available in a once-daily oral formulation
  - PIONEER 6 study, patients randomized to oral semaglutide OD or placebo.
  - Primary endpoint **MACE** (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) **was reduced by 21%** (*P*< 0.001)
  - Death from **cardiovascular disease was significantly reduced (-51%)** with oral semaglutide, nonfatal myocardial infarction (+18%), or nonfatal stroke (–26%) did not differ significantly between groups.
  - **Death from any course was significantly reduced with oral semaglutide (–49%)**

- **Combination:**
  - Cargri-sema (Cargrilintide 2.4mg and Sema 2.4mg)

STEP trial programme (primary Obesity)

- **In STEP 1** - overweight or obesity **without T2D** receiving semaglutide **(n = 1,306)** once-weekly subcutaneous semaglutide **plus lifestyle intervention** - to week 68
- 52-week **off-treatment extension** phase of STEP 1 (n = 327), **weight regain in both treatment** arms resulting in net weight loss of 5.6% with semaglutide 2.4 mg and 0.1% with placebo

- **STEP 2** - **T2D** and overweight or obesity, once-weekly subcutaneous semaglutide 2.4 mg (n = 404) plus lifestyle intervention
- **STEP 3 - without DM, IBT +** semaglutide and an initial **low-calorie diet**, once-weekly subcutaneous semaglutide 2.4 mg (n = 407)

STEP 3 (placebo-subtracted weight loss 10.3%) vs. STEP 1 (placebo-subtracted weight loss 12.4%),

the inclusion of an intensive lifestyle intervention (including a partial meal replacement program and 30 treatment sessions) provided only a modest contribution to additional weight loss beyond that achieved with semaglutide and less intensive lifestyle intervention.

- In **STEP 5,** once-weekly subcutaneous semaglutide 2.4 mg (n = 152) resulted in substantial initial body weight reductions that were then **maintained over 104 weeks** compared to placebo. There **was no additional weight loss between weeks 52–104;** weight loss was maintained during this period. The mean weight loss in the semaglutide group was –15.2%, compared to –2.6% in the placebo group

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

N ENGL J MED 384;11 NEJM.ORG MARCH 18, 2021

STEP 1 trial

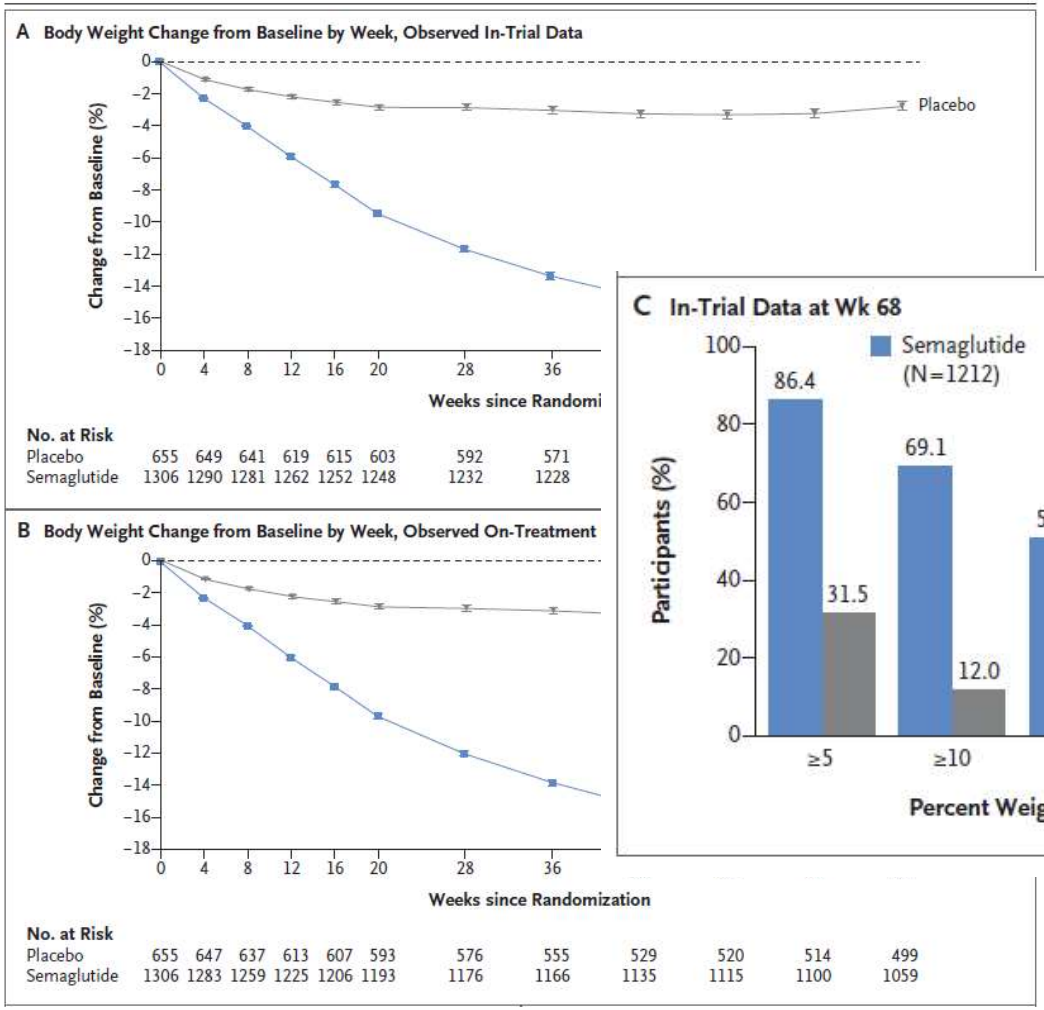
Once-Weekly Semaglutide in Adults with Overweight or Obesity

- **1961 adults** with a body-mass index >30, 2:1 ratio, **68 weeks**
- once-weekly *subcutaneous* semaglutide (**dose of 2.4 mg**) or placebo, plus **lifestyle intervention**.
- The co-primary end points were the percentage **change in body weight** and weight **reduction of at least 5%** (ITT style analysis)

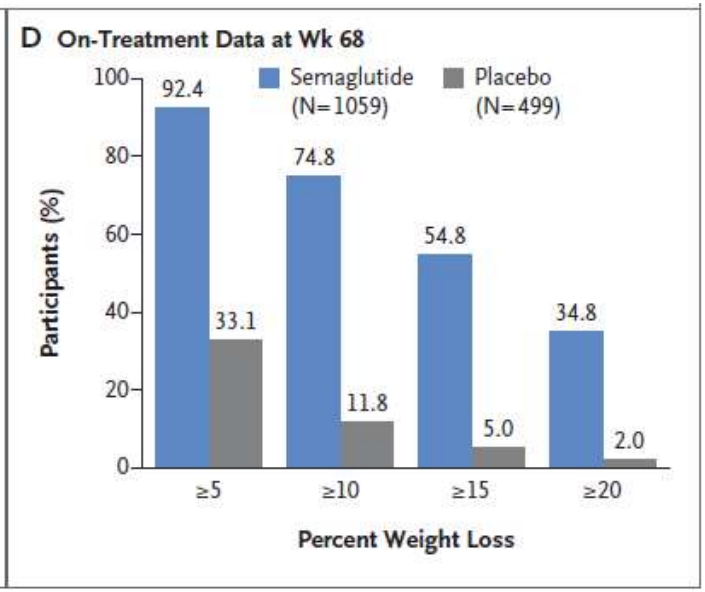
- **Results:** The mean change in body weight from baseline to week 68 was **-14.9%** in the semaglutide group as compared with **-2.4%** with placebo, for an estimated treatment difference of **-12.4** % (95% confidence interval [CI] -13.4 to -11.5; P<0.001).
- The change in body weight from baseline to week 68 was **-15.3** kg in the semaglutide group as compared with -2.6 kg in the placebo group (estimated treatment difference**, -12.7 kg;** 95% CI, -13.7 to -11.7)

- Participants who received semaglutide had a greater improvement in cardiometabolic risk factors and a greater increase in physical functioning
- *Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time*

- **Conclusions:** 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with **sustained, clinically relevant** reduction in body weight.
- (Funded by Novo Nordisk; STEP 1)


A Body Weight Change from Baseline by Week, Observed In-Trial Data
Change from Baseline (%)
0
−2
−4
−6
−8
−10
−12
−14
−16
−18
Placebo
0 4 8 12 16 20 28 36
Weeks since Randomi
No. at Risk
Placebo 655 649 641 619 615 603 592 571
Semaglutide 1306 1290 1281 1262 1252 1248 1232 1228
B Body Weight Change from Baseline by Week, Observed On-Treatment
Change from Baseline (%)
0
−2
−4
−6
−8
−10
−12
−14
−16
−18
0 4 8 12 16 20 28 36
Weeks since Randomization
No. at Risk
Placebo 655 647 637 613 607 593 576 555 529 520 514 499
Semaglutide 1306 1283 1259 1225 1206 1193 1176 1166 1135 1115 1100 1059

C In-Trial Data at Wk 68
Participants (%)
100
80
60
40
20
0
Semaglutide (N=1212)
Placebo (N=577)
86.4
31.5
69.1
12.0
50.5
4.9
32.0
1.7
≥5 ≥10 ≥15 ≥20
Percent Weight Loss


D On-Treatment Data at Wk 68
Participants (%)
100
80
60
40
20
0
Semaglutide (N=1059)
Placebo (N=499)
92.4
33.1
74.8
11.8
54.8
5.0
34.8
2.0
≥5 ≥10 ≥15 ≥20
Percent Weight Loss

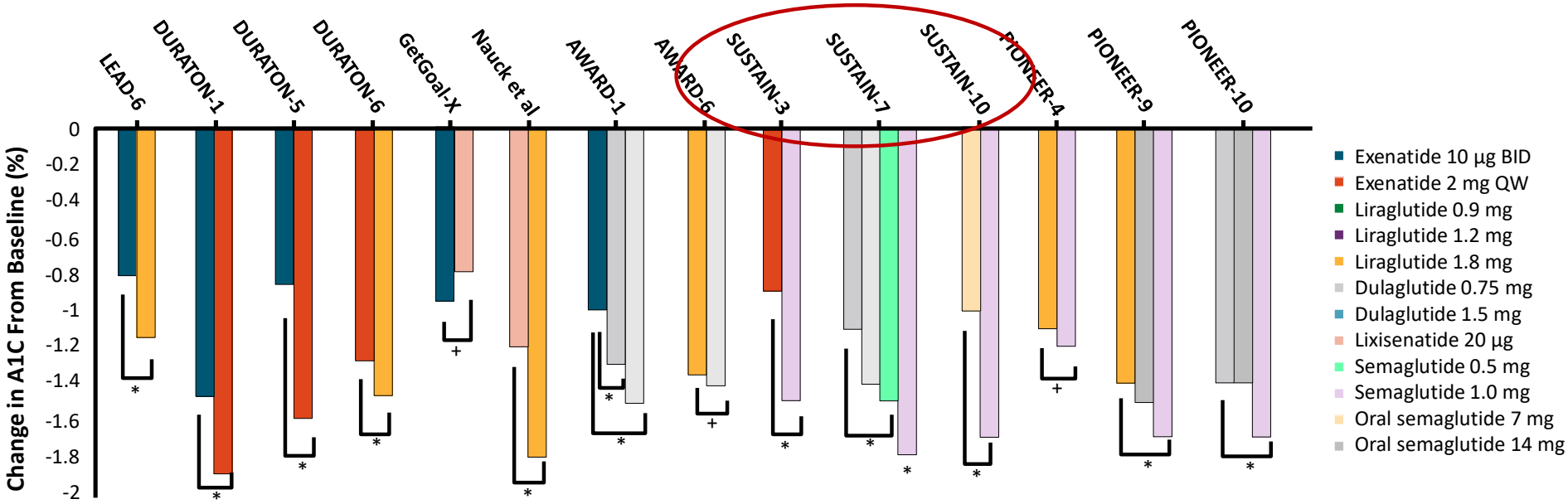
Risks and side effects - Semaglutide

- **pancreatitis** have been described in connection with the use of GLP-1RAs
- STEP 1 to 5 trials - history or presence of chronic pancreatitis or acute pancreatitis within the past 180 days **excluded**
- consensus statement: GLP-1RAs should be used cautiously (if at all) in patients with a history of pancreatitis (due to a lack of clinical trial data), and that treatment should be discontinued if acute pancreatitis develops

- Weight loss is known to increase the risk of **cholelithiasis,** prevalence reaching 12% after 8 - 16 weeks of a low-calorie diet and reaching greater than 30% within 12 - 18 months after gastric bypass surgery
- GLP-1RA treatment has been linked with an increase in gallbladder AEs, including cholelithiasis and cholecystitis
- In STEP 1, 3, and 5, gallbladder-related disorders were reported in a higher proportion of participants in the semaglutide 2.4 mg groups

- The prescribing information for semaglutide state that they have been reported to cause **thyroid C-cell tumors in rodents**
- A meta-analysis of 11 cardiovascular outcomes studies of GLP-1RAs including over **55,000 patients** identified **no increased risk** of MTC with GLP-1RAs No cases of MTC were reported in STEP 1 to 5, no imbalances in calcitonin levels between semaglutide 2.4 mg and the placebo group

GLP-1 RA Comparative **Studies in T2D**: Change in A1C



*P <.05. †P <.05, meeting predefined noninferiority margin.

Figure adapted from: Trujillo. Ther Adv Endocrinol Metab. 2021;12:2042018821997320. Note that direct comparisons between clinical trials cannot be made. Ahmann. Diabetes Care. 2018;41:258. Blevins. J Clin Endocrinol Metab. 2011;96:1301. Buse. Lancet. 2009;374:39. Buse. Lancet. 2013;381:117. Capehorn. Diabetes Metab. 2020;46:100. Drucker. Lancet. 2008;372:1240. Dungan. Lancet. 2014;384:1349. Nauck. Diabetes Care. 2016;39:1501. Pratley. Lancet. 2019;394:39. Pratley. Lancet Diabetes Endocrinol. 2018;6:275. Rosenstock. Diabetes Care. 2013;36:2945. Wysham. Diabetes Care. 2014;37:2159. Yabe. Lancet Diabetes Endocrinol. 2020;8:392. Yamada. Lancet Diabetes Endocrinol. 2020;8:377.

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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*

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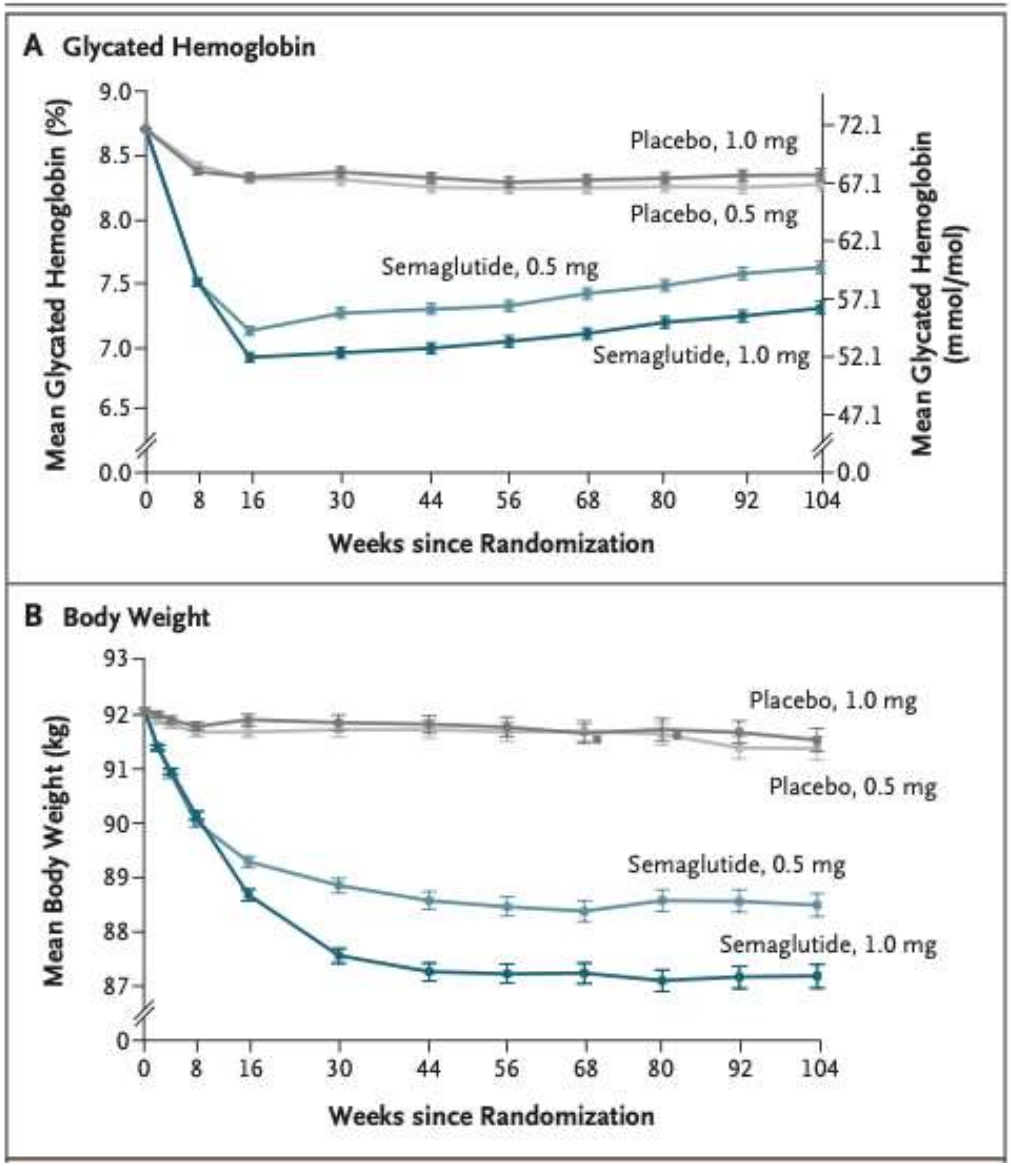
- **3297** patients with **type 2 diabetes** - on a standard-care regimen, once-weekly semaglutide
- randomized either **0.5 mg or 1.0 mg or placebo**
- *fixed dose-escalation procedure was used, with a starting dose of 0.25 mg for 4 weeks that escalated to 0.5 mg for 4 weeks until the maintenance dose (0.5 mg or 1.0 mg) was reached*
- primary composite outcome - first occurrence of **cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke**
- Cox proportional-hazards model with pooled treatment (semaglutide vs. placebo)
- median observation time was 2.1 years

- Rates of premature treatment discontinuation were similar across groups (20% overall)
- The primary outcome occurred in **108 of 1648 patients (6.6%) in the semaglutide group** and in **146 of 1649 patients (8.9%)** in the placebo group (hazard ratio, 0.74; **0.58 to 0.95;** P<0.001)
- Nonfatal myocardial infarction occurred in 2.9% (hazard ratio, 0.74; 95% CI, **0.51 to 1.08;** P=0.12);
- nonfatal stroke occurred in 1.6% (hazard ratio, 0.61; 95% CI, **0.38 to 0.99**; P=0.04)

  - worsening nephropathy were lower in the semaglutide group,
  - **rates of retinopathy complications** (vitreous hemorrhage, blindness, requiring treatment with an intravitreal agent or photocoagulation) were significantly higher


A Glycated Hemoglobin
Mean Glycated Hemoglobin (%)
9.0
8.5
8.0
7.5
7.0
6.5
0.0
72.1
67.1
62.1
57.1
52.1
47.1
0.0
Mean Glycated Hemoglobin (mmol/mol)
Placebo, 1.0 mg
Placebo, 0.5 mg
Semaglutide, 0.5 mg
Semaglutide, 1.0 mg
0 8 16 30 44 56 68 80 92 104
Weeks since Randomization
B Body Weight
Mean Body Weight (kg)
93
92
91
90
89
88
87
0
Placebo, 1.0 mg
Placebo, 0.5 mg
Semaglutide, 0.5 mg
Semaglutide, 1.0 mg
0 8 16 30 44 56 68 80 92 104
Weeks since Randomization

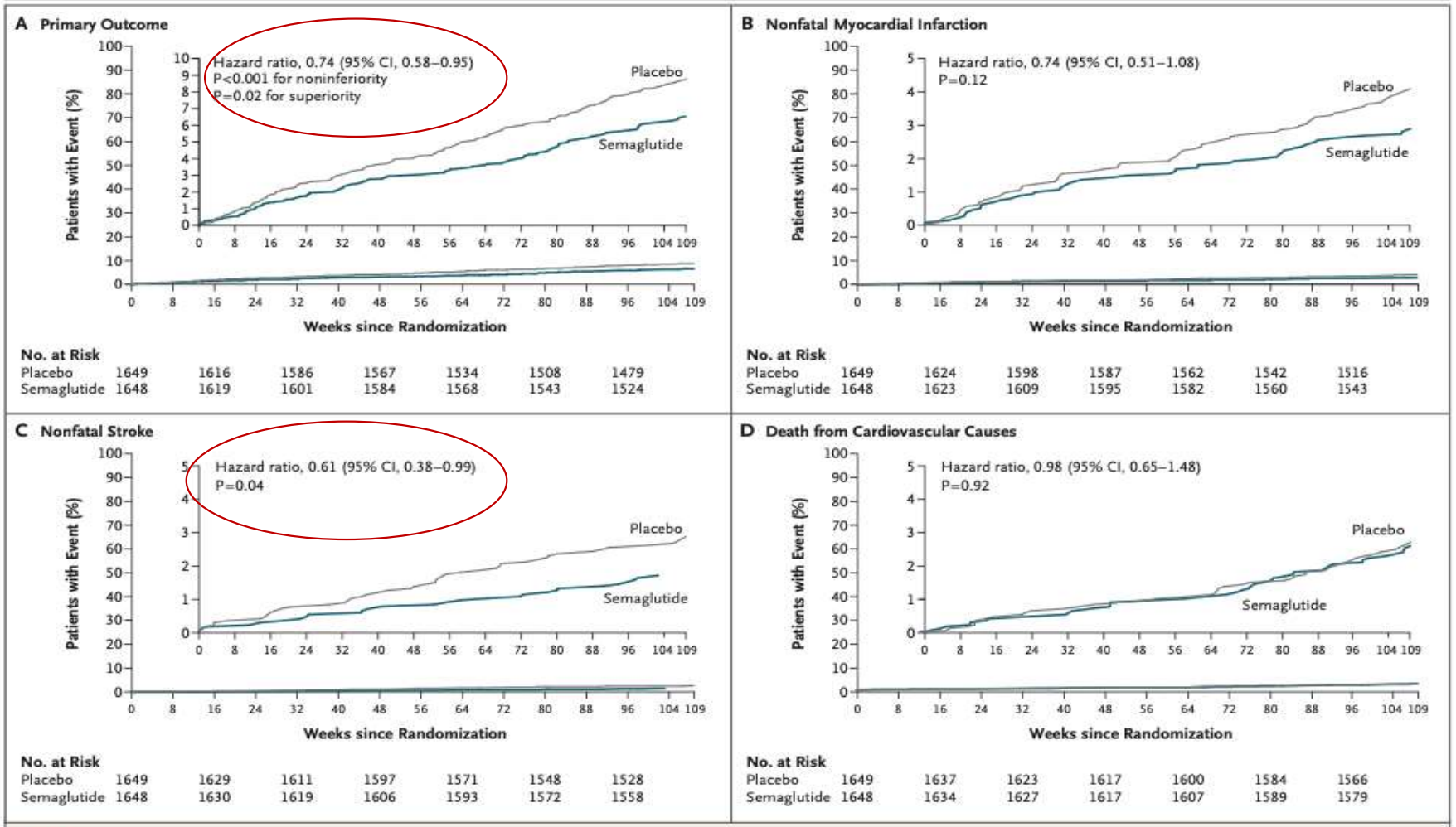
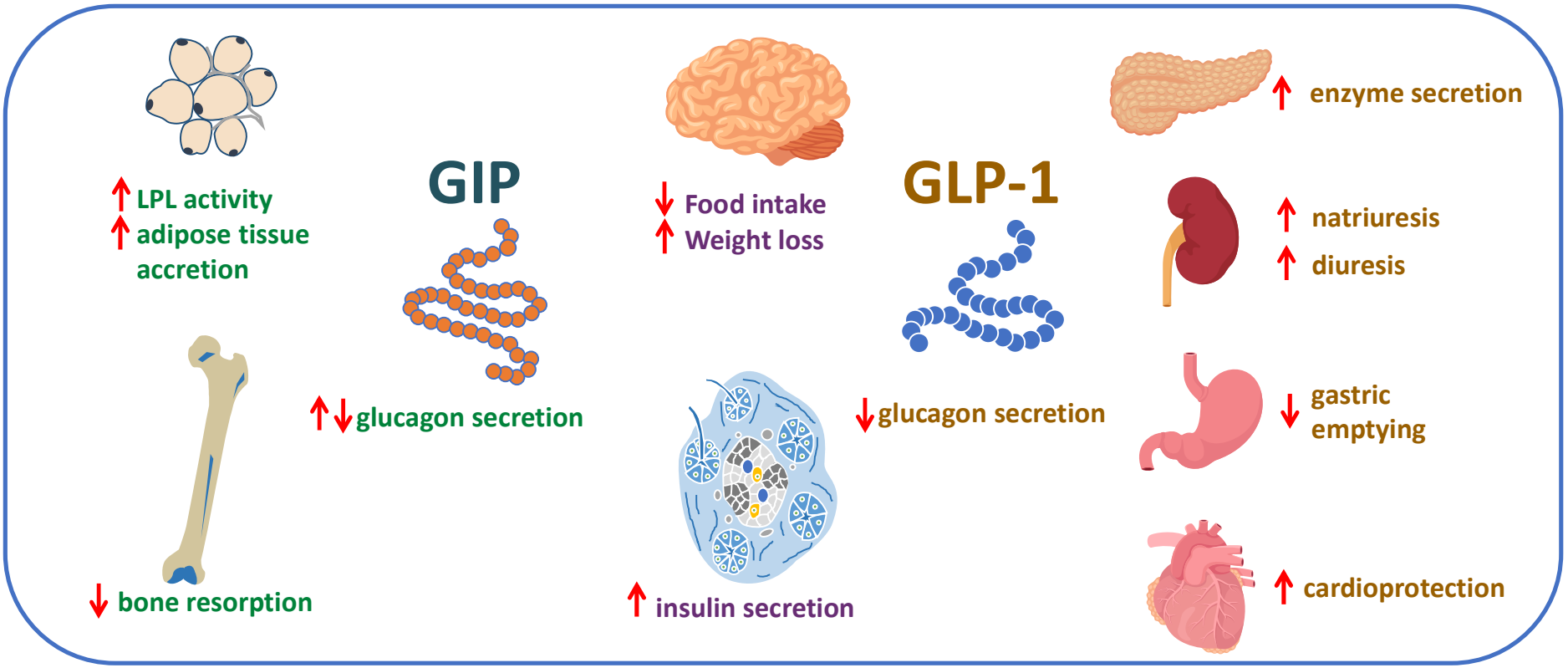


Figure 1. Cardiovascular Outcomes.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

The Evolving GIP–GLP-1 Partnership in Metabolism



Baggio. J Mol Metabolism. 2020;46:101090.

GIP - MECHANISM OF ACTION (1)

- **GIP Enhances the Lipid-Buffering Capacity of WAT**
  1. GIP receptor is expressed in WAT
  2. increase LPL activity
  3. acutely clear dietary triglyceride (TAG)
  4. reduces lipid ‘spillover’ and ectopic fat accumulation in tissues such as liver, skeletal muscle, heart, and pancreas
  5. GIP promotes TAG storage following food intake
  6. by hypertrophy of existing adipocytes

- stimulates glucose uptake - enhance insulin-stimulated glucose uptake
- improves whole-body insulin sensitivity and lowers hepatic lipid accumulation

GIP - MECHANISM OF ACTION (2)

- **GIP - Act in the CNS to Lower Food Intake and Reduce Body Weight**
- GIP-R is widely expressed within the CNS - in areas implicated in regulating energy balance
- crossing the blood–brain barrier to access sites of action

1. GIP action in the CNS - reducing energy consumption, *especially when combined with GLP-1*
2. GIP and GLP-1 COMBINED - more robust anorexia and weight-lowering than the individual agents

- **GIP-R agonism attenuates the emetic responses characteristic of the gut peptide PYY**
- enhance GLP-1R-mediated weight loss by **increasing tolerance**

GIP- CONANDRUM

- GIP is the **predominant incretin**, highlighting the importance of GIP in insulin secretion
- concerns that the lipogenic effects of GIP could promote weight gain

- GIP and GLP-1 have opposing effects on the counter-regulatory hormone **glucagon**
  - because GLP-1 decreases, whereas GIP increases its secretion
- T2DM acute co-administration of GIP and GLP-1 has a neutral effect on glucagon

Glucagon-like Peptide-1 Receptor Agonism

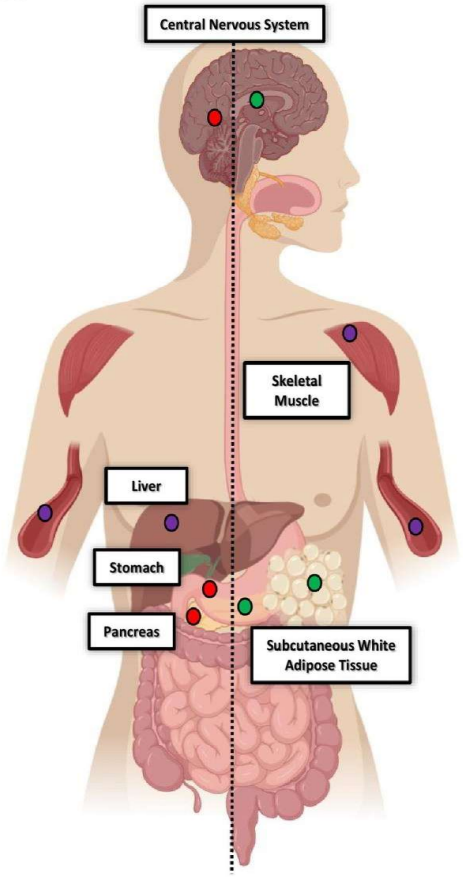
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

Trends in Endocrinology & Metabolism

Tirzepatide: Novel Dual GIP and GLP-1 Receptor Agonist

- Tirzepatide is 39 amino acid peptide based on **native GIP peptide** sequence and modified to **bind to GIP or GLP-1 receptors**

- Administered as once-weekly injection as **half-life of 5 days**
  - Starting dose 2.5 mg weekly, titrated at 2.5-mg increments monthly to **max dose of 15 mg**

- Contraindications and AEs similar to GLP-1 RAs (dulaglutide)
  - Contraindications: personal or family history of MTC or MEN2
  - Precautions: pancreatitis, AKI, diabetic retinopathy, gallbladder disease
  - Adverse events: GI including nausea, vomiting, diarrhea, constipation, abdominal pain

Min. Diabetes Ther. 2021;12:143. Coskun. Mol Metab. 2018;18:3. Tirzepatide PI.

Tirzepatide trials

- SURPASS – for DM – 7 + 1 CVOT

- SURMOUNT – for weight loss
  - 1= weight
  - 2 = DM2
  - 4 = maintenance
  - MMO-CV = CV outcome trial